No. 2012-1120

In the United States Court of Appeals for the Federal Circuit

BIOGEN IDEC INC. and GENENTECH, INC.,

Plaintiffs-Appellants,

v.

GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED,

Defendants-Appellees.

Appeal From The United States District Court For The Southern District Of California In Case No. 10-CV-0608, The Honorable Roger T. Benitez.

OPENING BRIEF OF PLAINTIFFS-APPELLANTS BIOGEN IDEC INC. AND GENENTECH, INC.

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April 11, 2012

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UNITED STATES COURT OF APPEALS FOR THE FEDERAL CIRCUIT

BIOGEN IDEC V. GLAXOSMITHKLINE, 2012-1120

Certificate of Interest

Counsel for Appellants Biogen Idec Inc. and Genentech, Inc. certifies the following to the best of his knowledge:

1. The full name of every party or amicus represented by me is:

   Biogen Idec Inc.
   Genentech, Inc.

2. The names of the real party in interest (if the party named in the caption is not the real party in interest) represented by me is:

   N/A

3. All parent corporations and any publicly held companies that own 10 percent or more of the stock of the party or amicus curiae represented by me are:

   For Biogen Idec Inc.: None

   For Genentech, Inc.: Genentech, Inc.; Roche Holdings, Inc.; Roche Holding, Ltd.; Novartis AG; Novartis International Ltd.

4. The names of all law firms and the partners or associates that appeared for the party or amicus now represented by me in the trial court or agency or are expected to appear in this court are:

   DLA Piper LLP (US): John Allcock, Stanley J. Panikowski, Kathryn Riley Grasso, Aaron G. Fountain, and Erica J. Pascal

   Steptoe & Johnson LLP: Meredith Martin Addy, Rama C. Elluru

Dated: April 11, 2012

Stanley J. Panikowski

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I. STATEMENT OF RELATED CASES

No appeal in or from this action was previously pending before this Court or any other appellate court. Counsel is aware of no other case pending in this or any other court that will directly affect or be directly affected by this Court's decision in the pending appeal.

II. JURISDICTIONAL STATEMENT

The district court had jurisdiction over this patent infringement action based on 28 U.S.C. §§ 1331 and 1338(a). On November 15, 2011, the district court entered a final judgment of non-infringement under Federal Rule of Civil Procedure 54(b) and stayed all further proceedings pending the outcome of this appeal. (JA 1-2.) Patentees Biogen Idec Inc. and Genentech, Inc. filed a notice of appeal from this judgment on December 5, 2011. (JA 1115-1119.) This Court has jurisdiction over this appeal under 28 U.S.C. § 1295(a)(1).

III. STATEMENT OF THE ISSUE

Whether the district court erred in rejecting the plain and ordinary meaning of the claim term "anti-CD20 antibody"—an antibody that binds to a cell surface CD20 antigen—by improperly finding a prosecution history disclaimer and further limiting the claims based on features of the accused product.

IV. PRELIMINARY STATEMENT

In the mid-1990s, scientists and physicians from Biogen Idec Inc. and Genentech, Inc. (together "Patentees") discovered that patients suffering from a

common, incurable cancer called Chronic Lymphocytic Leukemia ("CLL") could be treated effectively using "anti-CD20 antibodies." Defying scientific doubt and uncertainty, the discovery revolutionized the treatment of CLL patients. Anti-CD20 antibodies specifically target a protein known as "CD20" on the surface of certain cancer cells. As a result, anti-CD20 antibodies are significantly less deleterious than more traditional CLL treatments like chemotherapy and radiation which indiscriminately bombard a patient's body with toxic chemical compounds. In recognition of their innovation, Biogen Idec and Genentech were awarded U.S. Patent No. 7,682,612 (the "'612 patent").

The '612 patent covers the Patentees' novel method of treatment: administering a therapeutically effective amount of anti-CD20 antibody to a human CLL patient. The invention is focused on the discovery that CLL patients may be treated with anti-CD20 antibodies, and the independent claims therefore are not limited to any particular anti-CD20 antibody. The specification likewise teaches the use of anti-CD20 antibodies to treat CLL and defines "anti-CD20 antibody" as any antibody that specifically recognizes the cell surface CD20 antigen. The prosecution history also gives the term its full breadth; the Examiner construed the term to include "any and all" anti-CD20 antibodies, and Patentees never disagreed.

The district court, however, rejected the plain and ordinary meaning of "anti-CD20 antibody"—*i.e.*, an antibody that binds to a cell surface CD20 antigen.

Disregarding the heavy presumption that a claim term should be given its plain and ordinary meaning, the court imposed limitations that are found nowhere in the intrinsic record. Under the district court's construction, an "anti-CD20 antibody" not only must bind to a cell surface CD20 antigen, it also must bind to that antigen with a particular "specificity" and "affinity," and even to a particular "epitope" on the surface of the antigen.

Bypassing the claims and specification, the district court relied on only two sources to justify its erroneous limitations. First, the court isolated and misinterpreted four sentences from Patentees' response to an enablement rejection and erroneously ruled that these statements amounted to a prosecution history disclaimer. Nothing in these cherry-picked statements, however, suggests Patentees may have surrendered claim scope—much less comes close to the "clear and unmistakable" disavowal that this Court's precedent requires. Second, the court used extrinsic evidence about later-discovered features of the accused product to exclude that product from the scope of the '612 patent's claims. Using the accused product to narrow the scope of the claims violates this Court's precedent and constitutes improper reliance on extrinsic evidence.

Here, the accused infringer failed to overcome the heavy presumption that claim language is given its plain and ordinary meaning. Nowhere did Patentees "clearly and unambiguously" disavow any claim scope from "anti-CD20

antibodies." In fact, the intrinsic record shows repeatedly that Patentees used this term consistent with its plain and ordinary meaning. This Court therefore should reject the district court's improperly narrow construction, construe "anti-CD20 antibody" according to its plain meaning—"an antibody that binds to a cell surface CD20 antigen"—vacate the judgment of noninfringement that is based solely on the district court's erroneous construction, and remand the case for further proceedings.

V. STATEMENT OF THE CASE

Patentees filed this patent infringement action against Defendants GlaxoSmithKline LLC and Glaxo Group Limited (collectively, "GSK") in the United States District Court for the Southern District of California in March 2010. (JA 28, 73-79.) Patentees asserted claims 1-4, 6, 8-10, 14-17, 20-22, and 58-60 of U.S. Patent No. 7,682,612 ("the '612 patent"). (JA 4.) GSK counterclaimed, alleging non-infringement, invalidity, and unenforceability of the '612 patent. (JA 29-30.)

The parties disputed the construction of three pairs of claim terms, including "anti-CD20 antibody" and "CD20-binding fragment." The district court issued its claim construction order on October 18, 2011. To facilitate an immediate appeal of this claim construction ruling, the parties stipulated to non-infringement and the court entered judgment under Federal Rule of Civil Procedure 54(b) on November

15, 2011. (JA 1-2.) The district court stayed all remaining proceedings pending the outcome of this appeal. (JA 2.) Patentees filed their notice of appeal on December 5, 2011. (JA 1115-1119.)

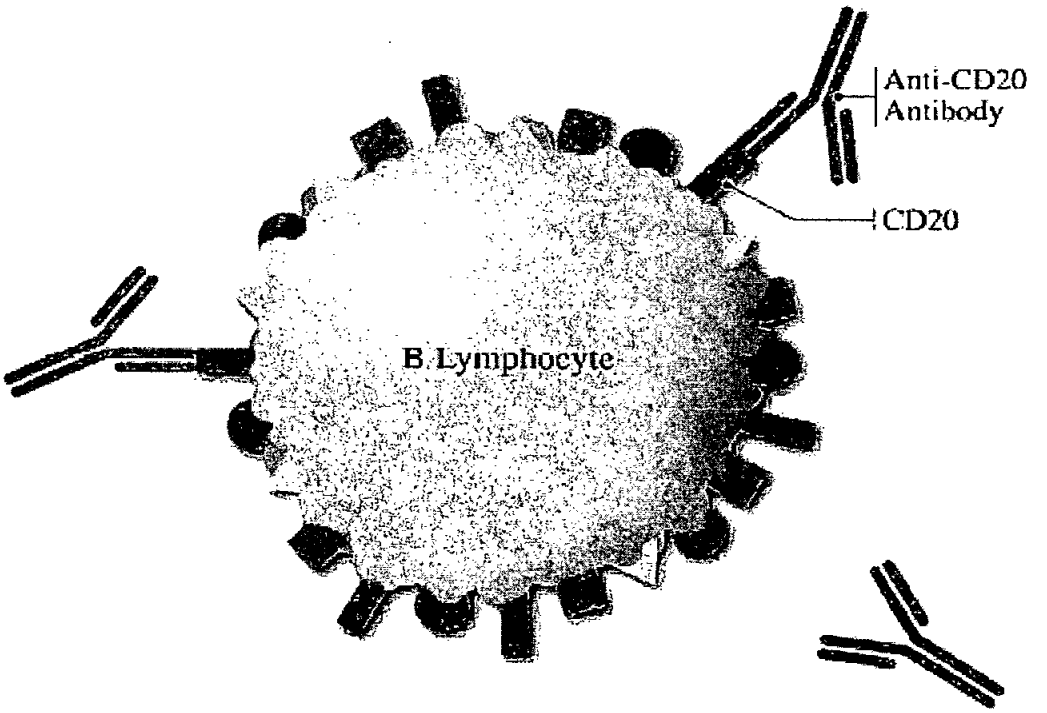
VI. STATEMENT OF FACTS

A. The '612 Patent Discloses The Use Of Anti-CD20 Antibodies To Effectively Treat Patients With Chronic Lymphocytic Leukemia.

U.S. Patent No. 7,682,612 (the "'612 patent") covers Patentees Genentech's and Biogen Idec's breakthrough discovery that anti-CD20 antibodies can be used to effectively treat patients with a blood cancer known as chronic lymphocytic leukemia ("CLL"). As described below, this discovery surprised the scientific community and revolutionized the treatment of this common and deadly disease.

CLL is a cancer in which a type of white blood cell called a B lymphocyte ("B cell") becomes cancerous. (JA 619.) A single B cell undergoes a change—a "malignant transformation"—that causes it to replicate, and B cells accumulate in the bloodstream and certain tissues to much higher levels than present in a healthy person. (JA 620-621.) The body's mechanisms for controlling the normal growth, proliferation, and death of B cells fail. (JA 621.) The unabated proliferation of B cells—*i.e.*, cancerous B cells—leads to an accumulation of cancerous cells in the blood and bone marrow of CLL patients. (JA 619.) Unabated proliferation of B cells also occurs in other types of cancers, including B-cell lymphomas (cancer of the lymph nodes). ('612 patent at 1:27-28, JA 44; JA 617, 619.)

At the time of the '612 patent, anti-CD20 antibodies were already known in the art and were used as therapeutic agents to treat B-cell malignancies other than CLL. ('612 patent at 1:23-25, JA 44.) The CD20 antigen is a protein that is expressed on the cell surface of both normal and cancerous B cells. (JA 635, 636.) The CD20 protein is embedded in the outer membrane of the cell such that part of the CD20 protein is exposed on the outer surface of the cell (*i.e.*, this part is "extracellular"). (JA 635.)



(JA 636.)

An antibody is a protein that is capable of binding to a specific "target" that is often a protein itself. (JA 632.) The anti-CD20 antibodies are engineered to "target" CD20 antigens by specifically recognizing and binding to the part of the

antigen that is on the surface of the B cell, and eventually destroying the cell. (JA 632-633, 636.) Anti-CD20 antibodies destroy both normal and cancerous B cells, but the human body makes new normal B cells to replace the ones depleted by treatment with anti-CD20 antibodies. (JA 636.)

Prior to the '612 patent, anti-CD20 antibodies were known to be used as a diagnostic and therapeutic agent for B-cell lymphomas. ('612 patent at 1:23-25, JA 44.) The Food and Drug Administration had approved the therapeutic use of one such anti-CD20 antibody, Patentees' RITUXAN® (rituximab), for use in the treatment of relapsed and previously treated low-grade non-Hodgkins lymphoma ("NHL"), a type of B-cell lymphoma. ('612 patent at 1:41-45, 48-51, JA 44.)

Although the use of anti-CD20 antibodies to treat NHL was known at the time of the '612 patent application, those skilled in the art did not reasonably expect the same therapeutic benefit to result from using anti-CD20 antibodies to treat CLL. (JA 1191-1192, 1196-1199.) Two fundamental differences between B-cell lymphomas (such as NHL) and CLL underscore why skilled scientists and physicians did not believe anti-CD20 antibodies would effectively treat CLL. (JA 1192, 1197-1198; '612 patent at 2:23-34, JA 44.)

First, in 1998, it was known that B cells from patients with NHL exhibit a high density of CD20 antigen, the "target" molecule. (JA 1192, 1197; '612 patent at 2:27-29, JA 44.) In other words, B cells from NHL patients have an abundance

of the CD20 antigen, which significantly increases the likelihood that the anti-CD20 antibodies will recognize and attach to CD20 in sufficient numbers to effect treatment. In contrast, B cells from CLL patients exhibit a low density of the CD20 antigen. (JA 1192, 1196; '612 patent at 2:27-29, JA 44.) The lower level of "target" CD20 antigen expression led scientists and physicians to believe that anti-CD20 antibodies could not bind to CLL B cells at sufficient density to achieve therapeutic benefits. (JA 1192, 1197.)

Second, CLL patients have a much higher number of circulating tumor cells in their blood than patients with NHL. (JA 1192, 1198; '612 patent at 2:26-27, JA 44.) Scientists and physicians expected the large number of circulating tumor cells to create a huge "sink" of CD20 binding sites in the blood of CLL patients. (JA 1192, 1198.) This "sink," in turn, would decrease the concentration of anti-CD20 antibodies in circulation and thereby render anti-CD20 antibody therapy ineffective in CLL patients. (JA 1192, 1198.) Scientists and physicians also believed that attacking so many circulating blood cells in a CLL patient was risky because killing so many circulating cells so quickly would cause harmful side effects, such as rapid tumor cell lysis. (JA 1202.)[1]

[1] In addition to having different cell biology, these different cancers (*i.e.*, NHL and CLL) affect different patient populations, have different clinical characteristics, differ in their typical progression and outcome, and respond differently to different therapies. (JA 1202.)

Defying conventional wisdom, Patentees' scientists and physicians discovered that the use of anti-CD20 antibodies is effective to treat CLL patients in a manner less toxic than conventional treatments like chemotherapy. The '612 patent covers this novel method of using anti-CD20 antibodies to effectively treat CLL patients.

B. The '612 Patent Claims Methods Of Using Anti-CD20 Antibodies To Effectively Treat Patients With Chronic Lymphocytic Leukemia.

The claims of the '612 patent cover methods of effectively treating CLL patients with anti-CD20 antibodies. ('612 patent at 7:63 to 10:51, JA 47-48.) Anti-CD20 antibodies themselves were known in the art at the time of the invention. The '612 patent does not claim their discovery. Nor does it claim a method of making anti-CD20 antibodies. Rather, the '612 patent claims methods of using anti-CD20 antibodies to effectively treat CLL patients.

1. The Independent Claims Are Not Limited To Any Particular Type Of Anti-CD20 Antibody.

Independent claims 1, 6, 23, 28, 58, and 60 all refer to treating CLL in a human patient by administering an "anti-CD20 antibody." ('612 patent at 7:63 to 10:51, JA 47-48.) These claims are not limited to the administration of a particular type of anti-CD20 antibody.[2] For example, independent claim 1 requires:

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[2] While the claims specifically exclude treatments using radiolabeled anti-CD20 antibodies, the "not ... radiolabeled" limitation is not at issue in this appeal.

> A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

('612 patent at 7:63-67, JA 47.)

2. The Dependent Claims Limit The Type Of Anti-CD20 Antibody Used In The Method.

By contrast, a number of the dependent claims are narrower with regard to the types of anti-CD20 antibodies used to treat the CLL patient. These include claims 11 and 33 ("wherein the anti-CD20 antibody is a *chimeric* antibody"[3]), claims 12 and 34 ("wherein the anti-CD20 antibody is *rituximab*"[4]), claims 13 and 35 ("wherein the anti-CD20 antibody is a *humanized* antibody[5]"), claims 14 and 36 ("wherein the anti-CD20 antibody is a *human* antibody"), and claims 15 and 37 ("wherein the anti-CD20 antibody comprises a CD20-binding fragment of a *chimeric, humanized, or human* antibody"). ('612 patent at 8:31-31, 9:31-41, JA 47-48 (emphasis added).)

When Patentees intended to limit the method claims to the use of certain types of anti-CD20 antibodies, they specified them in the dependent claims. And

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[3] A "chimeric" antibody refers to an antibody with non-human and human regions, most typically rodent and human regions. ('612 patent at 2:53-56, JA 44.)

[4] "Rituximab" is a chimeric anti-CD20 antibody. ('612 patent at 3:18-20, JA 45.)

[5] A "humanized" antibody refers to an antibody with substantially human regions. ('612 patent at 2:62-67, JA 44.)

none of the '612 patent's claims—independent or dependent—contains any limitation related to the concepts of "specificity," "affinity," or "epitope." ('612 patent at 7:63 to 10:51, JA 47-48.) In fact, those words do not appear in the claims at all.

C. The '612 Patent Specification Teaches The Use Of Anti-CD20 Antibodies To Effectively Treat CLL Patients.

The '612 patent specification confirms the nature of the invention: using anti-CD20 antibodies to effectively treat CLL patients. The specification discloses that the claimed invention is based on the surprising and unexpected discovery that the administration of a therapeutic anti-CD20 antibody treats certain malignancies (including CLL) characterized by high numbers of tumor cells in the blood. ('612 patent at 2:16-34, JA 44.) It teaches that the invention "comprise[s] the administration of a therapeutically effective amount of an anti-CD20 antibody." ('612 patent at 2:35-38, JA 44.)

The specification also identifies the preferred embodiments of the anti-CD20 antibodies used in the claimed methods. It states:

> In the preferred embodiment, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from 10^{-5} to 10^{-9} M. Preferably, the anti-CD20 antibody will comprise a chimeric, primate, PRIMATIZED®, human, or humanized antibody. Also, the invention embraces the use of antibody fragments, e.g., Fab's, Fv's, Fab's, $F(ab)_2$, and aggregates thereof.

('612 patent at 2:45-51, JA 44.)

The specification also explains that "[m]ethods for producing chimeric, primate, PRIMATIZED®, humanized, and human antibodies are well known in the art." ('612 patent at 3:1-3, JA 45.) It then incorporates by reference several patents directed at the production of antibodies. ('612 patent at 3:3-7, JA 45.)

The specification further discloses that "a particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab)." ('612 patent at 3:18-20, JA 45.) It also incorporates by reference the entirety of U.S. Patent No. 5,736,137 (the "'137 patent"), which teaches the isolation, screening and characterization of RITUXAN® in detail. The '137 patent defines an anti-CD20 antibody as "an antibody which specifically recognizes a cell surface . . . antigen . . . commonly referred to as CD20." ('137 patent at 6:65 to 7:2, JA 377-378.)

The '612 patent specification concludes with several examples, and cautions that they "are not intended, nor are they to be construed, as limiting the invention," but are "intended to provide clinical evidence in support of the efficacy of the invention." ('612 patent at 4:22-25, JA 45.) After providing the examples, the specification states: "Although the present invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding it will be apparent that certain changes and modifications may be practical within the scope of the appended claims." ('612 patent at 7:56-60, JA 47.)

D. The Examiner And Patentees Used The Ordinary Meaning Of "Anti-CD20 Antibody" In Making And Overcoming An Enablement Rejection.

During prosecution of the '612 patent, the PTO Examiner made an enablement rejection and withdrew it after Patentees' response. Both the Examiner's rejection and Patentees' response used the term "anti-CD20 antibody" in accordance with its plain and ordinary meaning. (JA 307-309; JA 324-326.)

1. The Examiner Understood "Anti-CD20 Antibody" According To Its Plain And Ordinary Meaning.

The Examiner initially rejected all pending claims under 35 U.S.C. § 112, ¶ 1 on the ground that "the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention." (JA 307.) The Examiner observed that the independent claims are "broadly drawn to '. . . an anti-CD20 antibody or fragment thereof'." (*Id.* (alteration in original).) The Examiner explained that "[t]his is broadly interpreted for examination purposes to be any and all anti-CD20 antibodies, no matter the specificity or affinity for the specific epitope on the circulating tumor cells." (*Id.*)

2. The Examiner's Enablement Rejection.

The Examiner first argued that "[w]hile the specification is enabling for the application of RITUXAN®, RITUXIMAB® and 2B8-MX-DTPA in the treatment of hematologic malignancies [*e.g.*, CLL], the specification is not enabling in the

application of all other anti-CD20 antibodies, which may have different structural and functional properties." (*Id.*) The Examiner explained that

> *selection* of an antibody as an immunotherapeutic agent is an unpredictable task as the antibody must possess sufficient specificity and a high degree of affinity for its target for use as an immunotherapeutic agent and because these qualities are dependent on the physiology of the particular pathology and the accessibility of the target antigen.

(*Id.* (emphasis added).) The Examiner contended:

> The specification is silent concerning what sort of specificity and affinity would be necessary for the antibodies of the claimed passive immunotherapy so that one skilled in the art would not be able to practice the claimed invention without undue experimentation.

(*Id.*)

Second, even though the method of treatment claims are not directed to *making* antibodies, the Examiner argued that the specification did not enable the making of all anti-CD20 antibodies covered by the broad scope of the claims. The Examiner stated that "the specification has not taught how one skilled in the art would make the necessary chimeric, humanized or human anti-CD20 antibody for use as a human therapeutic, i.e. one that would avoid the formation of antibodies against the foreign mouse antibodies." (JA 308.)[6]

[6] The Examiner lastly argued that the specification did not include certain teachings relating to the type of carrier or adjuvant to be used and what dosages would be effective. (JA 308.) Patentees also overcame this part of the enablement rejection and it is not at issue in this appeal.

The Examiner concluded that "[i]t would require undue experimentation of one skilled in the art to make and use all anti-CD20 antibodies that would be possibly effective in the treatment of a hematologic malignancy." (JA 308.) The Examiner did not require or suggest any amendment of the claims relating to the term "anti-CD20 antibody." (JA 307-309.)[7]

3. Patentees' Response To The Enablement Rejection.

Patentees responded to each basis of the Examiner's enablement rejection with arguments based on the disclosures in the '612 specification. Conspicuously, Patentees did not argue that the Examiner should interpret "anti-CD20 antibody" more narrowly than its plain meaning. To the contrary, Patentees agreed with the Examiner that the claims encompassed all anti-CD20 antibodies that could effectively treat CLL and argued that the full scope of the claims is enabled. Patentees never amended or narrowed the claim term "anti-CD20 antibody." (JA 317-337.)

Patentees first addressed the Examiner's concern that the "selection of an antibody as an immunotherapeutic agent is an unpredictable task" because different antibodies may have "different structural and functional properties." (JA

[7] The Examiner also explained the reasons for rejecting the ". . . fragment thereof [*i.e.*, of an anti-CD20 antibody]" portion of the claims. (JA 308-309.) At the Examiner's suggestion, Patentees amended the independent claims to add "antigen binding fragment." (JA 309; JA 318-319, 322.) Patentees ultimately removed the "fragment" limitation and instead used "CD20-binding fragment" in dependent claims 15 and 37 of the issued patent. ('612 patent at 8:39-41, 9:39-41, JA 47-48.)

307.) Patentees explained that "even though antibodies directed to the same antigen might have different affinities and functional characteristics, one of skill in the art could readily identify an antibody that binds to CD20 with similar affinity and specificity as does RITUXAN® [*i.e.*, an anti-CD20 antibody] using techniques that are well known in the art." (JA 324.) Citing the '137 patent as an example, Patentees stated:

> With that knowledge [of the '137 patent] in hand, the skilled artisan could readily produce anti-CD20 antibodies using similar techniques, and screen such antibodies for those having an affinity and *functional activity similar to* RITUXAN®. They would only need the motivation to do so, which the present invention provides.

(JA 324-325 (emphasis added).) Patentees explained that, in light of this disclosure, "no further description of anti-CD20 antibodies is required" to enable the broad scope of the method of treatment claims. (JA 325.) Patentees also noted the disclosure of a preferred embodiment of an anti-CD20 antibody having an "affinity ranging from 10^{-5} to 10^{-9} M." (*Id.*) Patentees further noted:

> Moreover, it is clear from the disclosure that the specificity must be such that antibody therapy results in a reduction of circulating tumor cells. Thus, the affinity and specificity of the antibodies to be used in the present invention are made clear in the disclosure.

(JA 325-326.)

Patentees also responded to the Examiner's concern about selecting antibodies by emphasizing the nature of the invention:

> Indeed, the novelty of the presently claimed invention *does not lie in an anti-CD20 antibody per se*. Rather, a novel aspect of the presently claimed invention lies in the revelation that *anti-CD20 antibodies can be used to treat hematological malignancies*, which would not have been expected given the low expression of CD20 on these cells and the high numbers of circulating tumor cells characteristic of these disorders.

(JA 325 (emphasis added).)

Patentees next addressed the Examiner's contention about making "chimeric, humanized or human antibodies as to avoid an immune response against the foreign antibodies." (JA 326.) Patentees pointed out that "at page 5, fourth paragraph, the specification states that methods for producing chimeric, primate, PRIMATIZED®, humanized and human antibodies are well known in the art, and moreover several patents disclosing the requisite technology are incorporated by reference." (*Id.*)

Patentees once again emphasized the nature of the invention:

> Again, *the novelty of the presently claimed invention does not lie in a method of making therapeutic antibodies* (although antibodies to be designed in the future for use in the claimed methods would certainly be encompassed). Rather, the presently claimed invention concerns the use of such antibodies for the treatment of hematologic malignancies . . . .

(*Id.* (emphasis added).)[8]

Without limiting the scope of the claims, Patentees concluded that "disclosure may be found in the specification for *all* items which the Examiner has alleged were missing and are allegedly required for the specification to enable the presently claimed methods." (JA 328 (emphasis added).) Patentees further explained that "[m]ost of these items, i.e., methods of making antibodies, methods of screening for antibodies having a certain affinity and activity, and types of pharmaceutical carriers, were known in the art at the time the present invention was filed and could be readily employed by those of skill in the art in practicing the claimed methods." (*Id.*)

The Examiner subsequently withdrew the enablement rejection, and allowed all pending claims with no amendment whatsoever to the term "anti-CD20 antibody." (JA 342.)

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[8] Patentees addressed the Examiner's remaining bases of his enablement rejection (relating to carrier and dosage issues) by pointing to "page 7, first two full paragraphs, where appropriate pharmaceutical carriers are disclosed, and effective doses are disclosed (with the caveat that an effective dose will depend on the particular antibody, but that optimization would not require[] undue experimentation)." (JA 326.) Further, Patentees noted that "the specification provides at least two examples which report data from *in vivo* trials to illustrate the efficacy of the antibody treatment for patients suffering from hematological malignancies." (JA 327.)

E. During Claim Construction, GSK Focused On Differences Between One Of The '612 Patent's Preferred Embodiments And GSK's Later-Developed And Accused Anti-CD20 Antibody.

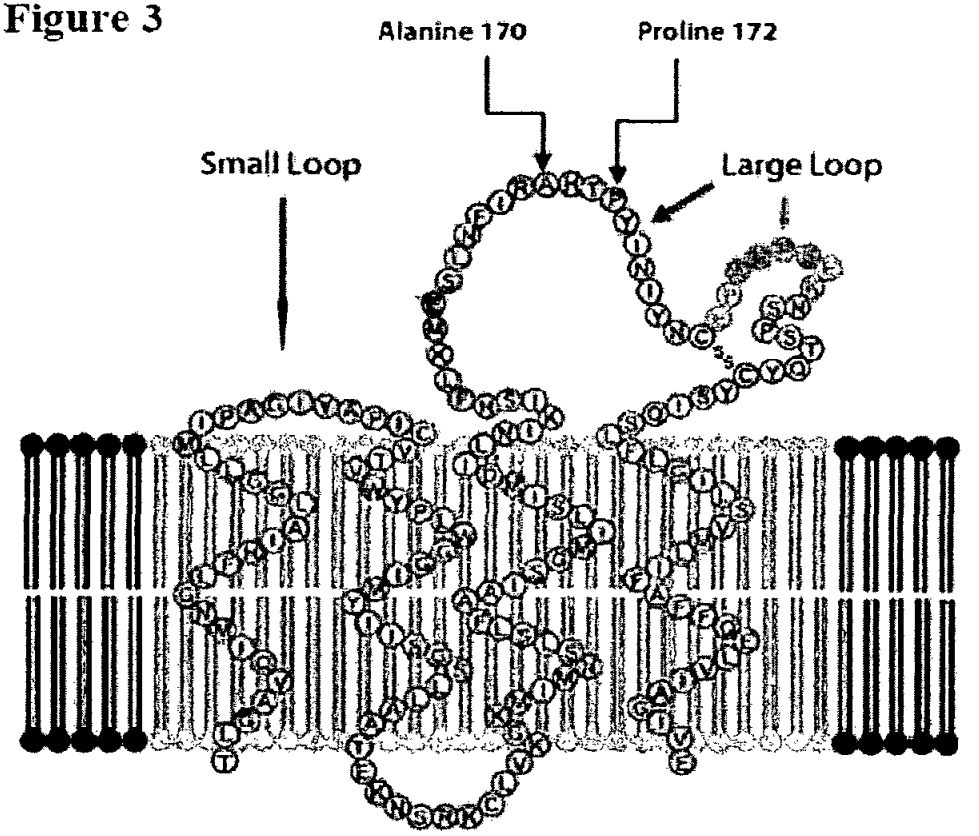
During claim construction, the parties disputed the meaning of "anti-CD20 antibody" and "CD20-binding fragment."[9] With respect to these two terms, GSK focused on the differences between the accused product, GSK's Arzerra®, and one of the '612 patent's preferred embodiments, rituximab (*i.e.*, Patentees' RITUXAN®). GSK noted that the RITUXAN® antibody was in part derived from mouse genes, whereas Arzerra®, developed in 2002, was a fully human antibody. (JA 695-697; JA 937, 948.) GSK also noted that the RITUXAN® antibody bound to a particular part (an "epitope") of the CD20 antigen, on the cell surface known as the "large loop" of the antigen. (JA692, 696.)

GSK explained that, in 2006, long after Arzerra® had been developed against the CD20 target, researchers determined the part ("epitope") of the CD20 antigen bound by Arzerra®. (JA 697, 709; JA 948.) GSK emphasized that this epitope was "distinct from the epitope that was bound by rituximab." (JA 697.) GSK further explained that this discovery demonstrated that CD20 had a second loop on the cell

[9] The claim construction issues relating to the clam terms "anti-CD20 antibody" and "CD20-binding fragment" are exactly the same. For convenience, therefore, the term "anti-CD20 antibody" is used throughout this brief to refer to both terms.

surface, which came to be known as the "small loop" of the CD20 antigen.[10] (JA 697.)

Figure 3



(JA 697.)

Based on this evidence, GSK argued that the '612 patent claim scope could not encompass an antibody with a characteristic that only subsequent research had discovered, *i.e.*, that Arzerra® binds to an epitope on the "small loop" of the CD20 antigen. (JA 693-694, 707, 710; JA 936-937, 945-946.) GSK further argued that

[10] GSK admitted that it had no knowledge of the epitope to which Arzerra® bound when it made Arzerra® in 2002. (JA 696-697.)

the '612 patent specification does not describe "any specific anti-CD20 antibody other than rituximab—a chimeric antibody" and that "all examples of the '612 patent pertain to the administration of rituximab to patients with cancers of the B lymphocytes." (JA 694, 707.) Even though the claims are not directed to the anti-CD20 antigen, but rather to certain therapeutic uses of anti-CD20 antibodies, GSK stressed that the '612 patent "fails to provide any information fully characterizing the CD20 antigen, including its topology or binding properties" "in any way [that] adds to the knowledge regarding CD20 found in the art as of 1998." (JA 694, 707-708.) GSK thus argued that "the phrase 'anti-CD20 antibody' refers to rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab." (JA 707, 710.)

F. The District Court Refused To Give "Anti-CD20 Antibody" Its Plain And Ordinary Meaning.

The district court narrowly interpreted the terms "anti-CD20 antibody" and "CD-20 binding fragment" to include *only* "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab."[11] (JA 16.) The district court relied heavily on its misunderstanding of four sentences from the prosecution history and on GSK's extrinsic evidence about

[11] The court stated: "But if you interpret the patent as broadly as you want me to interpret it, wouldn't that discourage people from, in fact, improving on your patent?" (JA 1079.) The court further stated: "[F]rom a policy perspective, it would seem to me there might be a difference in the way you construe a patent dealing with a medical drug, versus a transistor that you put in a radio." (JA 1084.)

its accused product, Arzerra®. (JA 13-16.) This extrinsic evidence included GSK's representation that Arzerra® bound to a second extracellular "loop" (the "small loop") of the CD20 antigen that was not known when the '612 patent application was filed. (JA 15-16.)

1. The District Court Found A Prosecution History Disclaimer As To The Term "Anti-CD20 Antibody."

The district court acknowledged that nothing in the claims or specification limited the term "anti-CD20 antibody" to any particular affinity, specificity, or epitope of the CD20 cell surface antigen. (JA 13.) The court recognized that the '612 patent specification discloses that "[t]he anti-CD20 antibody binds CD20, a protein found on the surface of the B lymphocytes." (*Id.*) Yet, the court concluded that "[t]he claims and the specification do not provide much guidance for whether the terms refer to an antibody or fragment thereof that binds to a particular epitope of the CD20 antigen with a particular affinity and specificity." (*Id.*)

The district court then determined that "[t]he clearest evidence of the meaning of 'anti-CD20 antibody' and 'CD20-binding fragment' comes from the prosecution history." (*Id.*) The court relied on four sentences across two excerpts of Patentees' response to the Examiner's enablement rejection:

> The Applicants argued that "even though antibodies directed to the same antigen might have different affinities and functional characteristics, one of skill in the art could readily identify an antibody that binds to CD20 with similar affinity and specificity as does RITUXAN®

> using techniques that are well known in the art." [JA 324.] In addition, the Applicants pointed out that "the specification defines the preferred antibody . . . as one that binds CD20 with an affinity ranging from 10^{-5} to 10^{-9} M. Moreover, it is clear from the disclosure that the specificity must be such that antibody therapy results in a reduction of circulating tumor cells. Thus, the affinity and specificity of the antibodies to be used in the present invention are made clear in the disclosure." [JA 325-326.]

(JA 14.)

Based on these excerpts and *Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313, 1326 (Fed. Cir. 2002), the district court concluded that "[t]he prosecution history establishes that 'anti-CD20 antibody' and 'CD20-binding fragment' are defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab." (JA 14.) The court thus ruled that the examples provided in the prosecution history statements amounted to a disclaimer of antibodies other than those with affinity and specificity similar to RITUXAN®. (JA 15.)

2. *In Limiting The Construction Of "Anti-CD20 Antibody," The District Court Relied On Extrinsic Evidence About The Features Of GSK's Later-Developed Accused Product.*

In addition to applying prosecution history disclaimer to narrow the claim term, the district court relied on extrinsic evidence in limiting "anti-CD20 antibody" to antibodies that bind to the same "epitope" of the CD20 antigen as rituximab. The court reasoned that:

> In 1998, at the time of the invention, it was believed that CD20 had only one extracellular region, or epitope, (i.e., the "large loop") to which CD20 antibodies could bind. Consequently, all antibodies that bound with a similar affinity and specificity as Rituxan would have been understood to bind to this epitope. Not until 2006 was it discovered that Arzerra, a human antibody, could bind to a previously unknown epitope of the CD20 antigen.

(JA 16.) After equating the concepts of "epitope" and "loop," the court related the concepts of "affinity and specificity" to the loop to which the antibody binds:

> The prosecution history establishes that "anti-CD20 antibody" and "CD20-binding fragment" is defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab. Antibodies that bind to the CD20 antigen with similar affinity and specificity as rituximab bind to the "large loop."

(*Id.*) Thus, even though Patentees did not limit their invention based on any particular loop or epitope of the CD20 antigen, the district court limited the terms "anti-CD20 antibody" and "CD20-binding fragment" to mean "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab." (*Id.*)

VII. SUMMARY OF ARGUMENT

The district court erred by rejecting the plain and ordinary meaning of "anti-CD20 antibody" and imposing limitations that are found nowhere in the intrinsic record. There is a heavy presumption that claim terms are given their plain and ordinary meaning. A challenger can overcome this presumption only by showing

that the patentee clearly disavowed claim scope. Here, the claims, specification, and prosecution history all use "anti-CD20 antibody" according to its plain and ordinary meaning: an antibody that binds to a cell surface CD20 antigen. The specification also includes an express definition of the term based on this plain meaning. Further, in the prosecution history, the Examiner and Patentees agreed that the claim term covered "any and all" anti-CD20 antibodies. The intrinsic evidence, therefore, unanimously confirms that the term should be given its plain and ordinary meaning.

The district court, however, bypassed the clear teachings of the claims, specification, and prosecution history to impose unfounded limitations on the claims. Specifically, the district court limited the term "anti-CD20 antibody" to Patentee's "particularly preferred" embodiment, RITUXAN®, and other anti-CD20 antibodies with similar "affinity," "specificity, and "epitope"-binding characteristics as RITUXAN®. The court imposed these limitations solely based on its misreading of four sentences in the prosecution history and GSK's extrinsic evidence concerning features of its accused product. In doing so, the court contradicted this Court's precedent and adopted an improperly narrow claim construction that should be reversed.

Nothing in the prosecution history suggests the Patentees departed from the plain and ordinary meaning of "anti-CD20 antibody," much less rises to the level

of the "clear and unmistakable" disavowal of claim scope that this Court's precedent requires for prosecution history disclaimer. Rather, the isolated statements on which the district court relied are simply part of Patentees' arguments to the Examiner that the specification's disclosure enables the *full scope* of the claims. Viewed both individually and in context, nothing in these statements amounts to an express relinquishment of scope from the plain and ordinary meaning of "anti-CD20 antibody." In fact, the prosecution history as a whole *confirms* that Patentees used the term according to its plain and ordinary meaning. The district court's "specificity," "affinity," and "epitope"-binding limitations were thus improper as a matter of law.

After finding a prosecution history disclaimer where none exists, the district court magnified its error by using extrinsic evidence of the accused product's features to support its "epitope"-binding limitation. The district court ruled that, because GSK later discovered that its Arzerra® drug binds to a part, or "epitope," of CD20's surface that was unknown when the '612 patent application was filed, the claims could not cover Arzerra®. This use of the accused product in claim construction was improper, and is an additional reason why the district court's construction should be rejected.

In sum, the intrinsic record reinforces the heavy presumption that "anti-CD20 antibody" should be given its plain meaning, and nothing in the intrinsic

record supports the district court's additional limitations. Accordingly, the district court's affinity, specificity, and epitope-binding limitations should be rejected, and "anti-CD20 antibody" should be given its plain meaning: an antibody that binds to a cell surface CD20 antigen. Because the stipulated judgment of noninfringement was based solely on the district court's incorrect claim construction, that judgment should be vacated and the case should be remanded for further proceedings under the correct construction.

VIII. ARGUMENT

A. Standard of Review.

The district court's claim construction is reviewed *de novo*. *Cybor Corp. v. FAS Techs., Inc.*, 138 F.3d 1448, 1454-55 (Fed. Cir. 1998) (en banc).

B. The District Court Erred By Refusing To Give The Term "Anti-CD20 Antibody" Its Plain And Ordinary Meaning.

The district court erred by narrowly construing the terms "anti-CD20 antibody" and "CD20-binding fragment." The claims, specification, and prosecution history all demonstrate that the term "anti-CD20 antibody" should be given its plain and ordinary meaning as "an antibody that binds to a cell surface CD20 antigen." Even the extrinsic evidence—to the extent it should be relied upon at all in this case—supports this plain-meaning construction. Likewise, the term "CD20 binding fragment" should be construed in accordance with its plain

and ordinary meaning as "a portion of an anti-CD20 antibody that binds to a cell surface CD20 antigen."[12]

1. The Claims Use "Anti-CD20 Antibody" Consistent With Its Plain And Ordinary Meaning.

Each asserted claim uses the term "anti-CD20 antibody" in accordance with its plain and ordinary meaning, an antibody that binds the CD20 cell surface antigen. *See Epistar Corp. v. Int'l Trade Comm'n*, 566 F.3d 1321, 1334 (Fed. Cir. 2009) (There is "a heavy presumption that claim terms carry their full ordinary and customary meaning." (citing *Omega Eng'g, Inc. v. Raytek Corp.*, 334 F.3d 1314, 1323 (Fed. Cir. 2003))); *Innogenetics, N.V. v. Abbott Labs.*, 512 F.3d 1363, 1370 (Fed. Cir. 2008) ("A plain reading of the claim limitation suggests that it does just what it says . . . ."). Claim 1 for example, covers:

> A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

('612 patent col.7, ll. 63-67.)

When Patentees intended to limit the treatment of CLL to the use of antibodies with particular characteristics, they did so by specifying those characteristics in the dependent claims. *See Phillips v. AWH Corp.*, 415 F.3d 1303,

[12] The issues on appeal are identical for both terms, so the remainder of the brief refers only to "anti-CD20 antibody" for convenience.

1314 (Fed. Cir. 2005) (en banc) ("[T]he context in which a term is used in the asserted claim can be highly instructive.") For example, claim 11 specifies the use of a chimeric anti-CD20 antibody, claim 12 recites the use of rituximab, claim 13 recites the use of a humanized anti-CD20 antibody, and claim 14 recites the use of a human anti-CD20 antibody. If Patentees had intended to limit the claims to anti-CD20 antibodies with particular epitope-binding, affinity, and specificity characteristics, they would have done so expressly in the claims. In fact, none of the claims suggests that the required anti-CD20 antibody is limited in any manner with regard to such characteristics. The words "epitope," "affinity" and "specificity" do not even appear in the claims.

The district court summarily dismissed the claims by stating that they "do not provide much guidance for whether the terms refer to an antibody or fragment thereof that binds to a particular epitope of the CD20 antigen with a particular affinity and specificity." (JA 13.) But the district court failed to recognize the obvious implication of the claims' silence regarding epitope, affinity, and specificity: Patentees used "anti-CD20 antibody" in accordance with its plain and ordinary meaning, without the extraneous claim limitations that the district court imposed.

2. The Specification Confirms That "Anti-CD20 Antibody" Should Be Given Its Plain And Ordinary Meaning.

The specification also teaches that "anti-CD20 antibody" should be given its plain and ordinary meaning. "[T]he specification 'is always highly relevant to the claim construction analysis. Usually, it is dispositive; it is the single best guide to the meaning of a disputed term.'" *Phillips*, 415 F.3d at 1315 (quoting *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996)).

The '612 specification defines "anti-CD20 antibody" according to its plain and ordinary meaning. The '612 specification expressly incorporates the '137 patent by reference. ('612 patent at 3:20-24, JA 45.) The specification of the '137 patent, in turn, expressly states:

> As used herein, the term "anti-CD20 antibody" is *an antibody which specifically recognizes a cell surface* nonglycosylated phosphoprotein of 35,000 Daltons, typically designated as the human B lymphocyte restricted differentiation *antigen* Bp35, *commonly referred to as CD20.*

('137 patent at 6:65 to 7:2, JA 377-378 (emphasis added).) This definition, of course, is part of the '612 specification. *See Cook Biotech Inc. v. Acell, Inc.*, 460 F.3d 1365, 1376 (Fed. Cir. 2006) ("'Incorporation by reference provides a method for integrating material from various documents into a host document . . . by citing such material in a manner that makes clear that the material is effectively part of the host document *as if it were explicitly contained therein.*'" (emphasis added)

(quoting *Advanced Display Sys., Inc. v. Kent State Univ.*, 212 F.3d 1272, 1282 (Fed. Cir. 2000))). Patentees therefore expressly told a person of ordinary skill in the art what they meant by "anti-CD20 antibody": an antibody that recognizes the CD20 antigen on the surface of the B cell.

The '612 specification further teaches that the "target" of the administered "anti-CD20" antibody is the CD20 antigen, not a particular epitope of this antigen. For example, the specification teaches that the invention "involves the discovery that hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood may be effectively treated by the administration of a therapeutic anti-CD20 antibody." ('612 patent at 2:16-19, JA 44.) At the time, this discovery was surprising for a number of reasons, including because the malignant tumor cells in diseases such as CLL (1) are present in very high numbers circulating in the blood and (2) do not express high densities of the CD20 antigen. ('612 patent at 2:22-32, JA 44.) There are a lot of cancerous B cells, but each B cell has relatively few CD20 targets on its surface. "Consequently, it could not have been reasonably predicted that the CD20 antigen would constitute an appropriate target for therapeutic antibody therapy of such malignancies." ('612 patent at 2:32-34, JA 44.) The specification thus makes clear that the "target" of the claimed treatment methods is simply "the CD20 antigen," not a particular epitope of this antigen. (*See* '612 patent at 1:15-19, JA

44 ("The present invention is directed to the treatment of hematologic malignancies associated with high numbers of circulating tumor cells by the administration of a therapeutically effective amount of a chimeric or humanized antibody that binds to the B-cell surface antigen Bp35 (CD20).").)

The specification also teaches that a variety of anti-CD20 antibodies may be used to target the CD20 cell surface antigen in the claimed treatment methods. In doing so, the specification does not express *any* intent—much less the clear expression of intent that the law requires—to *limit* the claims to the preferred embodiments. *See, e.g.*, *Laryngeal Mask Co. v. Ambu A/S*, 618 F.3d 1367, 1372 (Fed. Cir. 2010); *Golight, Inc. v. Wal-Mart Stores, Inc.*, 355 F.3d 1327, 1331 (Fed. Cir. 2004). The specification states:

> In the *preferred embodiment*, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from 10^{-5} M to 10^{-9} M. Preferably, the anti-CD20 antibody will comprise a chimeric, primate, PRIMATIZED®, human, or humanized antibody.

('612 patent at 2:45-49, JA 44 (emphasis added).) The specification discloses that methods for producing these different antibodies are well known in the art, and the specification incorporates four exemplary patents by reference. ('612 patent at 3:3-7, JA 45.) Following this broad disclosure of a variety of antibodies that are suitable for use in treating CLL patients, the specification identifies rituximab as a "*particularly preferred* chimeric anti-CD20 antibody." ('612 patent at 3:18-20, JA

45 (emphasis added).) The '612 specification in no way limits the scope of the term "anti-CD20 antibody" based on specificity, affinity, or the epitope to which the antibody binds.

The district court erred in bypassing the specification's teachings about the ordinary meaning of the term "anti-CD20 antibody," including the definition expressly set forth in the incorporated '137 patent. Nowhere does the specification suggest that *only* anti-CD20 antibodies with affinities and specificities similar to rituximab may be used. Nor does the specification suggest that an anti-CD20 antibody must bind to a particular epitope of CD20. Rather, the specification uses "anti-CD20 antibody" simply to denote an antibody with the defining characteristic that it targets the CD20 antigen on the surface of the B cells. This evidence is the "single best guide" to the meaning of "anti-CD20 antibody." *Phillips*, 415 F.3d at 1315.

3. Without Identifying A Clear And Unmistakable Disavowal, The District Court Erred In Ruling That Patentees Disclaimed The Plain And Ordinary Meaning Of "Anti-CD20 Antibody."

Consistent with the claims and specification, the prosecution history confirms that both the Examiner and Patentees understood "anti-CD20 antibody" to have its plain and ordinary meaning. To prove a disclaimer, GSK must "overcome a *heavy presumption* that claim terms carry their full ordinary and customary meaning, *unless* it can show the patentee *expressly relinquished* claim

scope." *Epistar*, 566 F.3d at 1334 (emphasis added). GSK must show that Patentees made disclaiming statements during prosecution that are "both so clear as to show reasonable clarity and deliberateness, and so unmistakable as to be *unambiguous evidence of disclaimer*." *Omega Eng'g*, 334 F.3d at 1325 (emphasis added) (internal citation omitted). Statements in the prosecution history that are subject to multiple reasonable interpretations cannot meet the high standard for a prosecution history disclaimer. *See, e.g.*, *Golight*, 355 F.3d at 1332; *N. Telecom Ltd. v. Samsung Elecs. Co.*, 215 F.3d 1281, 1293-95 (Fed. Cir. 2000). Contrary to the district court's ruling, nothing in the prosecution history amounts to the clear and unmistakable disavowal of claim scope that this Court requires for a prosecution history disclaimer.

a. The Examiner And Patentees Understood "Anti-CD20 Antibody" To Have Its Plain And Ordinary Meaning.

The Examiner's interpretation of the term "anti-CD20 antibody" is instructive. *See Salazar v. Procter & Gamble Co.*, 414 F.3d 1342, 1347 (Fed. Cir. 2005) ("Statements about a claim term made by an Examiner during prosecution of an application may be evidence of how one of skill in the art understood the term at the time the application was filed."). The Examiner expressly understood "anti-CD20 antibody" to have its plain meaning when he issued the enablement rejection:

> "an anti-CD20 antibody or fragment thereof" . . . is broadly interpreted for examination purposes to be *any and all* anti-CD20 antibodies, *no matter* the specificity or affinity for the specific epitope on the circulating tumor cells.

(JA 307 (emphasis added).)

Patentees did not disagree with the Examiner's broad interpretation of this term. Nor did they amend this claim term to overcome the enablement rejection, even though they made other amendments in response to the office action, including other aspects of the enablement rejection. Patentees instead argued that the '612 patent specification enabled the full scope of the claims based on the understanding that an "anti-CD20 antibody" is simply an antibody that binds to a cell surface CD20 antigen. In response, the Examiner withdrew the enablement rejection without suggesting that the enablement requirement would be satisfied only by narrowing the scope of the claim term "anti-CD20 antibody."

b. Reliance On Disclosed Methods Of Selection And Screening Of Anti-CD20 Antibodies And Preferred Embodiments Is Not A Disclaimer.

In responding to the Examiner's enablement rejection, Patentees referred to disclosure in the specification to show how it enables the full scope of the claimed methods. The Examiner posited that antibodies directed to the same antigen, CD20, might have different affinities and functional properties, and that selection of a therapeutic antibody is an unpredictable task as the antibody must possess

sufficient specificity and a high degree of affinity for its target. (JA 307.) In response, Patentees focused on disclosure that teaches the use of antibodies that bind to the CD20 antigen.

Patentees argued that the '612 patent specification enables isolating and selecting antibodies that bind to the CD20 antigen. In responding to the Examiner's "unpredictable task" concern, Patentees argued that isolating and screening for anti-CD20 antibodies was already known in the art, such as disclosed in the '137 patent, incorporated by reference in the '612 patent. Patentees showed that one of skill could identify antibodies that bind to CD20 with similar affinity and specificity as RITUXAN®, a preferred embodiment. Specifically, Patentees argued that one of skill in the art could use known isolation, screening and characterization techniques for one antibody, here RITUXAN®, to readily identify, screen, *and thus use*, other anti-CD20 antibodies having an affinity and "functional activity similar to RITUXAN®" (*i.e.*, those that bind to the CD20 antigen.) (JA 324-325 (emphasis added).) Patentees expressly stated that the '137 patent describes the isolation, screening, and characterization of RITUXAN® in such detail that "no further description of anti-CD20 antibodies is required." (JA 325.) At no point, however, did Patentees suggest—much less clearly and unmistakably state—that they were carving out and disavowing any claim scope from the plain meaning of "anti-CD20 antibody."

To further support their argument that the '612 specification enables the full claim scope, Patentees pointed to the disclosure that "the specificity must be such that antibody therapy results in a reduction of circulating tumor cells." (*Id.*) Patentees also noted the disclosure of a preferred embodiment having an "affinity ranging from 10^{-5} to 10^{-9} M." (*Id.*) But once again, they did so *in support of* the full claim scope, not as an affirmative disavowal of unreferenced subject matter within the plain meaning of "anti-CD20 antibody."

The district court, therefore, erred in limiting the required "anti-CD20 antibody" based on one isolated reference to RITUXAN®. Far from limiting the scope of the invention, when viewed in context, Patentees simply relied on the discussion of the preferred embodiment to show that the disclosure enabled the use of anti-CD20 antibodies. Their use of examples of the preferred embodiment was not a clear and unmistakable disavowal of all possible embodiments outside these examples.

c. Other Statements In The Same Office Action Response Contradict The District Court's Disclaimer Ruling.

Patentees' complete response to the enablement rejection establishes that Patentees and the Examiner understood the term "anti-CD20 antibody" to mean any antibody that binds to the cell surface CD20 antigen and that Patentees did not disavow any claim scope. The language identified by the district court as a

disclaimer is surrounded by statements that contradict, and thus preclude, the district court's ruling. *See Elbex Video, Ltd. v. Sensormatic Elecs. Corp.*, 508 F.3d 1366, 1372 (Fed. Cir. 2007) (noting "the potential for such ambiguities" in prosecution history and concluding that other statements in an office action response contradicted the district court's disclaimer ruling); *see also Bradford Co. v. Conteyor N. Am., Inc.*, 603 F.3d 1262, 1270 (Fed. Cir. 2010) ("'[T]he prosecution history provides evidence of how the [PTO] *and the inventor* understood the patent.'" (emphasis added) (quoting *Phillips*, 415 F.3d at 1317)).

Patentees explained to the Examiner that because the invention was the discovery that anti-CD20 antibodies could treat CLL, the claims were not limited to any particular type of anti-CD20 antibody:

> Indeed, the novelty of the presently claimed invention *does not lie in an anti-CD20 antibody per se*. Rather, a novel aspect of the presently claimed invention *lies in the revelation that anti-CD20 antibodies can be used to treat hematological malignancies*, which would not have been expected given the low expression of CD20 on these cells and the high numbers of circulating tumor cells characteristic of these disorders.

(JA 325 (emphasis added).)

Patentees also made clear that the '612 specification enables the use of antibodies other than RITUXAN® because the knowledge for producing and identifying such antibodies was already known in the art. (JA 326 (arguing that the specification enables the methods for producing "chimeric, primate,

PRIMATIZED®, humanized and human antibodies" that avoid an immune response against the foreign antibodies).) Patentees further explained that "antibodies to be designed in the future for use in the claimed methods would certainly be encompassed" by the claims. (*Id.*) Indeed, Patentees noted that the dosing levels of the anti-CD20 antibody depended on the "particular antibody" being administered, acknowledging that antibodies other than RITUXAN® may be used in the method claims. (*Id.*)

These statements during prosecution show that, far from disavowing any claim scope, Patentees consistently used the plain and ordinary meaning of the term "anti-CD20 antibody" to respond to the enablement rejection. The prosecution history is thus consistent with the other intrinsic evidence that "anti-CD20 antibody" means any antibody that binds to the cell surface CD20 antigen.

d. Ambiguous Statements Do Not Support Prosecution Disclaimer.

The understanding of the prosecution history set forth above is at least a reasonable interpretation of Patentees' statements. However, even if this Court does not conclude that the prosecution history *affirmatively* supports the plain and ordinary meaning of "anti-CD20 antibody," the isolated and disconnected prosecution statements relied upon by the district court to find disclaimer are no worse than ambiguous. Given the public notice function of the claims and specification, prosecution history disclaimer does not apply "where the alleged

disavowal of claim scope is ambiguous." *See, e.g.*, *Golight*, 355 F.3d at 1332 ("Because the statements in the prosecution history are subject to multiple reasonable interpretations, they do not constitute a clear and unmistakable departure from the ordinary meaning of the [claim term]."); *N. Telecom*, 215 F.3d at 1293-95 (holding that prosecution disclaimer did not apply because inventors statements were amenable to multiple reasonable interpretations).

The district court based its disclaimer finding on Patentees' statements made in response to an enablement rejection. "[B]ecause the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Phillips*, 415 F.3d at 1317. Patentees made arguments in response to that rejection, but never suggested—much less clearly stated—that they had to narrow the scope of the claim term "anti-CD20 antibody" to satisfy the enablement requirement.

Moreover, as noted above, Patentees consistently and repeatedly emphasized that the novelty of the invention was the use of anti-CD20 antibodies to treat CLL:

- Indeed, the novelty of the presently claimed invention does not lie in an anti-CD20 antibody per se. Rather, a novel aspect of the presently claimed invention lies in the revelation that anti-CD20 antibodies can be used to treat hematological malignancies, (JA 325);

- Again, the novelty of the presently claimed invention does not lie in a method of making therapeutic antibodies (although antibodies to be designed in the future for use in the claimed methods would certainly

> be encompassed). Rather, the presently claimed invention concerns the use of such antibodies for the treatment of hematological malignancies and particularly for the treatment of CLL, (JA 326).

And Patentees made clear that "disclosure may be found in the specification for *all* items which the Examiner has alleged were missing and are allegedly required for the specification to enable the presently claimed methods." (JA 328 (emphasis added).)

Thus, taken together, the inventors' statements amount to a variety of arguments to establish enablement of the full scope of the claims, as interpreted by the Examiner, is enabled. None of these statements, whether in combination or in isolation, amounts to a clear and unmistakable surrender of claim scope that this Court's precedents require before a disclaimer can be found. *See, e.g.*, *Epistar*, 566 F.3d at 1334; *Elbex*, 508 at 1372-73; *Omega Eng'g*, 334 F.3d at 1325.

e. The One Case Relied Upon By The District Court Precludes A Finding Of Prosecution History Disclaimer.

The only case the district court relied on to support its disclaimer ruling actually precludes a finding of disclaimer. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*, 299 F.3d 1313 (Fed. Cir. 2002). *Teleflex* acknowledged the "heavy presumption" that claim terms carry their full ordinary and customary meaning. *Teleflex*, 299 F.3d at 1325. While recognizing that a patentee may choose to deviate from that ordinary meaning, the Court explained that such deviation occurs

only if "the applicant characterized the invention using words or expressions of manifest exclusion or restriction during the administrative proceedings before the Patent and Trademark Office." *Id.* at 1326. After examining the entire intrinsic record, the *Teleflex* Court held: "Neither the specification nor the prosecution history includes an expression of manifest exclusion or restriction demonstrating an intent to limit [the claim term]." *Id.* at 1327. As in *Teleflex*, neither the specification nor the prosecution history in this case includes an expression of manifest exclusion or restriction demonstrating an intent to limit the term "anti-CD20 antibody" beyond an antibody that binds the cell surface CD20 antigen.

4. The District Court Erred By Relying On Extrinsic Evidence To Inject The "Epitope" Limitation Into The Claims.

The district court further erred by relying on extrinsic evidence of the accused product's features to support its requirement that the claimed anti-CD20 antibody must "bind to the same epitope as rituximab." "[A] court may not use the accused product or process as a form of extrinsic evidence to supply limitations for patent claim language." *Wilson Sporting Goods Co. v. Hillerich & Bradsby Co.*, 442, F.3d 1322, 1330-31 (Fed. Cir. 2006); *see also Intel Corp. v. VIA Techs., Inc.*, 319 F.3d 1357, 1367 (Fed. Cir. 2003) ("When an analysis of intrinsic evidence resolves any ambiguity in a disputed claim term, it is improper to rely on extrinsic evidence to contradict the meaning so ascertained."). The district court's requirement that the claimed anti-CD20 antibodies must bind to the same epitope

of CD20 as rituximab does not appear *anywhere* in the intrinsic record. Rather, it is based on the district court's reliance on extrinsic evidence about the accused Arzerra® product. Moreover, the district court's "epitope" limitation impermissibly contradicts the intrinsic record, as well as the extrinsic evidence offered by both parties' experts.

Although the specification and prosecution history do not mention the epitope or epitopes of the CD20 antigen to which the claimed anti-CD20 antibodies bind, the district court stated: "In 1998, at the time of the invention, it was believed that CD20 had only one extracellular region, or epitope (i.e., the 'large loop') to which CD20 antibodies could bind." (JA 16.) The court apparently relied on the testimony of GSK's claim construction expert Dr. Deans for this point. The district court then reasoned:

> Consequently, all antibodies that bound with a similar affinity and specificity as Rituxan at the time of the invention would have been understood to bind to this epitope. *Not until 2006 was it discovered that Arzerra, a human antibody, could bind to a previously unknown epitope of the CD20 antigen, with a different affinity and specificity than rituximab.*

(*Id.* (emphasis added).)

The district court then improperly tethered the conclusion it drew from the extrinsic evidence to the prosecution history:

> Whether claim language may encompass after-arising technology, however, is irrelevant here. The prosecution

> history establishes that "anti-CD20 antibody" and "CD20-binding fragment" is defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab. Antibodies that bind to the CD20 antigen with similar affinity and specific as rituximab bind to the "large loop." Accordingly, the terms "anti-CD20 antibody" and "CD20-binding fragment" shall be construed as "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab" and "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," respectively.

(*Id.*)

The district court's analysis on this point is flawed in three key respects. First, the intrinsic evidence establishes that, in the '612 patent, "specificity" refers simply to whether an antibody binds to CD20 or whether it binds to some other antigen—*not* to which epitope of the CD20 antigen an anti-CD20 antibody binds. Second, the accused Arzerra® product, which was developed in 2002, is irrelevant to a skilled artisan's understanding of the '612 patent when it was filed in 1998. Third, neither party's expert offered an opinion supporting a construction that limits anti-CD20 antibody by epitope. Accordingly, the district court erred when it imported an epitope limitation from the extrinsic evidence into the claims.

a. Specificity Does Not Mean "Epitope."

In the context of the '612 patent, a person of ordinary skill in the art would understand the term "specificity" to refer to whether an antibody selectively targets

the CD20 cell surface antigen, not whether the antibody binds to a particular epitope of the CD20 cell surface antigen. The specification of the '612 patent explains that although "CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells," ('612 patent at 1:25-27, JA 44), "it could not have been reasonably predicted that the CD20 antigen would constitute an appropriate target for therapeutic antibody therapy of [hematologic] malignancies," ('612 patent at 2:31-34, JA 44). The incorporated '137 patent generally explains this "targeting" as follows:

> antibodies specific to the CD20 surface antigen of B cells are, e.g., injected into a patient. These anti-CD20 antibodies specifically bind to the CD20 cell surface antigen of (ostensibly) both normal and malignant B cells; the anti-CD20 antibody bound to the CD20 surface antigen may lead to the destruction and depletion of neoplastic B cells.

('137 patent at 3:30-36, JA 376.)

The '137 patent goes on to disclose that the only required feature of an anti-CD20 antibody is that it "specifically recognize[] a cell surface . . . antigen . . . , commonly referred to as CD20." ('137 patent at 6:65 to 7:2, JA 377-378.) During prosecution of the '612 patent, Patentees further explained that the only required specificity of the anti-CD20 antibody is "the specificity must be such that antibody therapy results in a reduction of circulating tumor cells." (JA 325.) Nothing in the

record suggests that only anti-CD20 antibodies that bind the same epitope of the CD20 antigen as rituximab result in a reduction of circulating tumor cells.[13]

Hence, the term "specificity" simply refers to the ability of an antibody to target the CD20 cell surface antigen. The term does not require binding to a particular epitope. The district court's construction therefore impermissibly contradicts the intrinsic evidence.

b. Arzerra® Is Irrelevant To Claim Construction.

The district court's reference to Azerra® and the knowledge of its binding properties learned in 2006 was prompted by GSK's argument that claims cannot be interpreted to cover discoveries made later than the claimed invention. This is incorrect for two reasons.

First, the structural differences between the preferred embodiment disclosed in the '612 patent and GSK's Arzerra® are irrelevant to the meaning of "anti-CD20 antibody." Throughout its claim construction arguments, GSK repeatedly emphasized the differences between Patentees' product, RITUXAN®, and GSK's own product, Arzerra®. But "a court may not use the accused product or process as

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[13] Even the researchers that discovered the accused Arzerra® product used "specificity" in the sense of targeting the CD20 antigen, not the targeting of a particular epitope on the CD20 antigen: "CD20 specificity was confirmed by *binding to CD20-expressing* NS-0 and SKBR3 *cells, but not to the nontransfected parent cells* and by cross blocking of a range of known CD20 mAbs (not shown). Thus by all criteria tested, these human mAbs were *specific for human CD20.*" (JA 842 (emphasis added).)

a form of extrinsic evidence to supply limitations for patent claim language." *Wilson Sporting Goods*, 442, F.3d at 1330-31. The only proper role of accused products in a claim construction analysis is to help focus construction on the terms most useful to facilitate that analysis. *Id.* at 1331. The district court's use of the accused product's features to decide the meaning of claim language thus ran afoul of this Court's precedent.

Second, this Court's precedent "allows for after-arising technology to be captured within the literal scope of valid claims that are drafted broadly enough." *Innogenetics*, 512 F.3d at 1371-72. In *SuperGuide Corp. v. DirecTV Enters., Inc.*, the Court expressly rejected the same argument that GSK makes here and concluded that the term "regularly received television signal" included digital television signals, even though "no televisions existed as of [the patent's filing date] that could receive digital signals." 358 F.3d 870, 878 (Fed. Cir. 2004) ("Method and apparatus claims not written in means-plus-function format are not necessarily limited to that disclosed in the specification but rather are defined by the language of the claims themselves."); *see also Innogenetics*, 512 F.3d at 1370 ("[A]s is well established, an applicant is not required to describe in the specification every conceivable and possible future embodiment of his invention."). The timing of Arzerra's discovery relative to the invention of the

'612 patent is irrelevant to the meaning of "anti-CD20 antibody" to a person of ordinary skill in the art as of the 1998 effective filing date of the '612 patent.

Moreover, the intrinsic evidence makes clear that the claims use "anti-CD20 antibody" in accordance with the term's ordinary and customary meaning, without limitation by the particular epitope to which it binds. A person of ordinary skill in the art as of the effective filing date of the '612 patent would appreciate that the specification plainly states that all that is required is that the anti-CD20 antibody target the CD20 cell surface antigen. (*See, e.g.*, '612 patent at 1:15-28, 2:32-34, JA 44; '137 patent at 3:30-36, 6:65 to 7:2, JA 376-378.) The realization in 2006 that an antibody discovered in 2002 binds to a different epitope of the CD20 antigen does not change the understanding of a person of ordinary skill in the art in 1998.[14]

[14] Although the district court did not expressly prohibit construing claims to cover after-arising technology, the district court's comments at the claim construction hearing are telling. In particular, the district court stated its concern that a broad construction of "anti-CD20 antibody" would discourage the development of after-arising technology as potential improvements of the claimed methods of treatment: "But if you interpret the patent as broadly as you want me to interpret it, wouldn't that discourage people from, in fact, improving on your patent?" (JA 1079.) Because of this concern, the district court stated, "[F]rom a policy perspective, it would seem to me there might be a difference in the way you construe a patent dealing with a medical drug, versus a transistor that you put in a radio." (JA 1084.) These statements strongly suggest that the district court's policy concerns drove its erroneous claim construction. "Claim construction, however, is not a policy-driven inquiry." *SmithKline Beecham Corp. v. Apotex Corp.*, 403 F.3d 1331, 1339 (Fed. Cir. 2005).

c. The Parties' Experts Agreed That The Term "Anti-CD20 Antibody" Is Not Limited By Epitope.

The extrinsic evidence ultimately does not support the district court's construction in any event. Both parties' experts agreed that the "epitope" limitation was not part of the claims. Dr. Deans, GSK's claim construction expert, testified that a person of ordinary skill in the art would understand the term anti-CD20 antibody to mean "any antibody that was produced originally in a mouse with endogenous immunoglobulin and transgenes directed against human CD20 extracellular epitopes."[15] (JA 575.) Although no party advocated this particular construction to the district court, it reflects Dr. Deans' understanding that the term "anti-CD20 antibody" is not limited according to the particular epitope of CD20 to which it binds. Patentees' expert, Dr. Coutré, similarly understood anti-CD20 antibody to mean an antibody "that can specifically recognize and bind to the CD20 found on the surface of B lymphocytes." (JA 636.) Because the parties' experts agree that the term anti-CD20 antibody is not limited by the epitope of CD20 to which the antibody binds, the extrinsic evidence itself undermines the district court's construction.

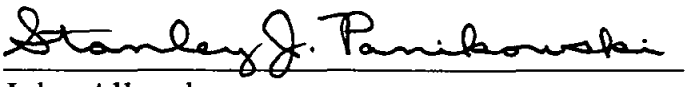
[15] In this context, "extracellular epitopes" simply means that the antibody binds to the CD20 antigen accessible on the surface of the cell. (JA 697 (showing two extracellular loops of the CD20 antigen).)

IX. CONCLUSION

The district court erred in limiting "anti-CD20 antibody" and "CD20-binding fragments" to "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab." Patentees respectfully ask the Court to reject the district court's construction, apply the plain meaning of the claim terms ("an antibody or antibody fragment that binds to a cell surface CD20 antigen"), vacate the judgment of noninfringement, and remand for further proceedings under the proper construction.

Dated: April 11, 2012

Respectfully submitted,



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UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BIOGEN IDEC, INC., and GENENTECH, INC., Plaintiffs, vs. GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED, Defendants.	CASE NO. 10-CV-00608 BEN (BGS) **ORDER GRANTING JOINT MOTION AND STIPULATION FOR FINAL JUDGMENT OF NON-INFRINGEMENT** [Docket No. 64]

The Court, having considered the Joint Motion and Stipulation of the parties, and having considered the concerns of judicial economy, finds that its October 18, 2011 Claim Construction Order is effectively a final adjudication of the Plaintiffs' claims of patent infringement against the Defendants, and that pursuant to Federal Rule of Civil Procedure 54(b) there is no just reason for delay in an appeal of that ruling. Therefore, the Court hereby **ORDERS, ADJUDGES AND DECREES**:

1. Judgment is hereby entered in favor of Defendants GlaxoSmithKline LLC and Glaxo Group Limited (collectively "Defendants" and "GSK"), and against Plaintiffs Biogen Idec, Inc. ("Biogen") and Genentech, Inc. ("Genentech") (collectively "Plaintiffs") on all claims asserted in Plaintiffs' First Amended Complaint;
2. Judgment is hereby entered in favor of Defendants and against Plaintiffs on Defendants' counterclaim for non-infringement;

3. All further proceedings in this Court, pending the outcome on appeal, are **STAYED**. Defendants will be allowed to assert all existing Counterclaims and Affirmative Defenses in their current form if this matter is remanded for further consideration. Plaintiffs will be allowed to assert their Claims in their current form to the extent applicable following remand and to rely on their current pleadings in response to Defendants' Counterclaims. The parties shall also have the right to amend their current pleadings to add additional claims or defenses as the Court allows, and shall be allowed to serve Final Infringement and/or Invalidity Contentions as provided in Patent Local Rule 3.6.

4. Each party will bear its own costs and attorneys' fees.

5. This is a final, appealable judgment.

IT IS SO ORDERED.

DATED: November 15, 2011

HON. ROGER T. BENITEZ
United States District Court Judge

UNITED STATES DISTRICT COURT
SOUTHERN DISTRICT OF CALIFORNIA

BIOGEN IDEC, INC., and GENENTECH, INC.,

Plaintiffs,

vs.

GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED,

Defendants.

CASE NO. 10-CV-00608 BEN (BGS)

CLAIM CONSTRUCTION ORDER

In this patent infringement action, the parties seek construction of three pairs of claim terms found in U.S. Patent No. 7,682,612. This matter was heard on June 9, 2011. Having considered the papers filed by the parties and oral argument on the motion, the Court construes the terms as follows.

BACKGROUND

Leukemia is a cancer of the white blood cell. In chronic lymphocytic leukemia ("CLL"), white blood cells known as B cells, or B lymphocytes, become cancerous. CLL patients have markedly increased numbers of B lymphocytes in the blood and bone marrow, and often in the lymph nodes and spleen. CLL is often diagnosed by measuring the number of B lymphocytes circulating in the blood. Symptoms of CLL include fatigue, fevers, bruising, bleeding, and infections. These symptoms are caused by the decrease in the number of red blood cells and platelets. In addition, the lymph nodes and spleen may enlarge due to the accumulation of cancerous B lymphocytes in these organs. The decision to treat a CLL patient is based upon the diagnosis of symptoms. The goals of treating CLL

are to (1) reduce the symptoms of the disease and (2) reduce the signs[1] of the disease. Treatment may also strive to increase the overall survival time of the patient as well as extend the amount of time the patient stays without signs or symptoms between treatments.

On November 9, 1999, Plaintiffs Biogen Idec, Inc. and Genentech, Inc. applied for U.S. Patent No. 7,682,612, which was approved on March 23, 2010. The '612 patent claims methods of treating CLL. The claimed invention consists of administering patients Rituxan, chimeric[2] anti-CD20 antibodies that recognize CD20 (a protein found on the outside surface of B lymphocytes) and destroy the cells that have CD20 on their surface. Rituxan is used in combination with conventional fludarabine and cyclophosphamide chemotherapy regimens.

On October 26, 2009, Defendants GlaxoSmithKline LLC and Glaxo Group Limited obtained FDA approval for Arzerra, its competing drug for treating CLL. Arzerra is a fully-human anti-CD20 antibody that binds with greater affinity[3] than Rituxan. In addition, Arzerra binds to a different epitope[4] than Rituxan—a portion of the CD20 antigen that was previously believed to be located beneath the cell surface. Arzerra is administered independently of other active anti-cancer agents.

Plaintiffs bring this action for infringement of the '612 patent. Specifically, Plaintiffs allege that the administration of Arzerra infringes claims 1–4, 6, 8–10, 14–17, 20–22, and 58–60 of the '612 patent. The parties have submitted competing constructions for three pairs of claim terms found in the '612 patent.

DISCUSSION

I. LEGAL STANDARD

"It is a bedrock principle of patent law that the claims of a patent define the invention to which the patentee is entitled the right to exclude." *Phillips v. AWH Corp.*, 415 F.3d 1303, 1312 (Fed. Cir. 2005) (internal quotation marks omitted). Courts determine the meaning of disputed claim terms from

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[1] "Symptoms" refers to what the patient experiences, while "signs" refers to the objective findings based on physical examinations or other tests performed on the CLL patient.

[2] A "chimeric antibody" is an antibody made from antibodies of more than one animal species.

[3] The "affinity" is how tightly an antibody attaches to a cell.

[4] An "epitope" is the location on the cell where an antibody attaches.

the perspective of a person of ordinary skill in the art at the time the patent is filed. *Chamberlain Group, Inc. v. Lear Corp.*, 516 F.3d 1331, 1335 (Fed. Cir. 2008). Claim terms "are generally given their ordinary and customary meaning." *Phillips*, 415 F.3d at 1312 (internal quotation marks omitted).

When construing claim terms, the court should first look to sources in the intrinsic record. *Vitronics Corp. v. Conceptronic, Inc.*, 90 F.3d 1576, 1582 (Fed. Cir. 1996). First, "the claims themselves provide substantial guidance as to the meaning of particular claim terms." *Phillips*, 415 F.3d at 1314. Second, the claims "must be read in view of the specification, of which they are a part." *Id.* at 1315 (internal quotation marks omitted). The specification is usually "dispositive," as "it is the single best guide to the meaning of a disputed term." *Id.* (internal quotation marks omitted). Third, the court should consider the patent's prosecution history, which is the record of proceedings before the Patent and Trademark Office ("PTO") and includes the prior art cited during the patent examination. *Id.* at 1317. However, "because the prosecution history represents an ongoing negotiation between the PTO and the applicant, rather than the final product of that negotiation, it often lacks the clarity of the specification and thus is less useful for claim construction purposes." *Id.*

If the intrinsic evidence resolves the ambiguity in the disputed claim terms, then "it is improper to rely on extrinsic evidence." *Vitronics*, 90 F.3d at 1583. If ambiguities in the claim terms remain, however, courts may consider extrinsic evidence. *Id.* at 1584. Extrinsic evidence includes expert testimony, inventor testimony, dictionaries, and scientific treatises. *Phillips*, 415 F.3d at 1317.

II. THE '612 PATENT

The '612 patent, entitled "Treatment of Hematologic Malignancies Associated with Circulating Tumor Cells Using Chimeric Anti-CD20 Antibody," was issued on March 23, 2010. Biogen and Genentech are the assignees of the '612 patent.

The disputed claim terms are found in claim 1. Claim 1 covers: "A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an *anti-CD20 antibody* to the patient in an *amount effective to treat the chronic lymphocytic leukemia*, wherein the method *does not include treatment with a radiolabeled anti-CD20 antibody*." (Pascal Decl., Exh. 1 ['612 Patent], at 7:63–67 (emphasis added).) The parties dispute three pairs of claim terms: (1) "amount effective to treat" / "effective to treat the chronic lymphocytic leukemia," (2) "anti-CD20 antibody" / "CD20-

binding fragment," and (3) "does not include treatment with a radiolabeled anti-CD20 antibody" / "radiation is not used." Each pair of terms will be addressed in turn.

A. "Amount Effective to Treat" / "Effective to Treat the Chronic Lymphocytic Leukemia"

The parties dispute the terms "amount effective to treat" and "effective to treat the chronic lymphocytic leukemia." Plaintiffs propose that the term "effective to treat the chronic lymphocytic leukemia" be construed, while Defendants propose that the term "amount effective to treat" be construed. Plaintiffs propose that the term be construed as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient," while defendants propose that it be construed as "includes amount of compound that achieves a reduction in circulating tumor cells."

As a preliminary matter, Plaintiffs contend that Defendants artificially limit the term to "amount effective to treat," which divorces the phrase from CLL, the target disease. The PTO and the inventors defined and discussed the entire term "effective to treat the chronic lymphocytic leukemia" during the prosecution history, and the entire phrase was added to the claims in an amendment, as explained in more detail below. (Pascal Decl., Exh. 5, at BID0004763.) In addition, the goal of the claimed method is to treat CLL specifically, as also explained below. Accordingly, the entire term "effective to treat the chronic lymphocytic leukemia" will be construed. *See Exxon Chem. Patents, Inc. v. Lubrizol Corp.*, 64 F.3d 1553, 1557 (Fed Cir. 1995) (claims must be construed in their entirety).

Before determining how the term "effective to treat the chronic lymphocytic leukemia" should be construed, it is also important to clarify the difference between the parties' proposed constructions. The parties agree that "effective to treat the chronic lymphocytic leukemia" includes the amount of antibody that achieves a reduction in circulating tumor cells; the issue is whether a patient *must also* reach a positive clinical benefit in order for the treatment to be effective. (*See* Pl. Op. Br. at 11 ("The claim-construction dispute addresses whether it is sufficient for the drugs at issue here *merely* to achieve a reduction in circulating tumor cells. Plaintiffs' construction . . . requires providing the patient with a positive clinical benefit that is directly related to the disease." (emphasis added)); Def. Op. Br. at 10 ("[Defendant]'s proposed construction does not foreclose the term 'amount effective to treat' from including treatment that results in partial or full remission of the disease, *i.e.*, positive

clinical benefit (according to plaintiffs). Rather, [Defendants] object[] to plaintiffs' limitation of the claim language to mean *only* treatment that results in a positive clinical benefit, (*i.e.*, partial or complete remission).").) At times, Defendants suggest that Plaintiffs' proposed construction excludes achieving a reduction in circulating tumor cells. (*See, e.g.*, Def. Op. Br. at 15 ("[P]laintiffs and their expert suggest that 'effective to treat' as used in the claims *does not include* a reduction in circulating tumor cells." (emphasis added)).) Plaintiffs' proposed construction, however, recognizes that the disputed term includes a reduction in tumor cells.

In addition, "positive clinical benefit" must be defined. The PTO considered the 1996 National Cancer Institute ("NCI") Guidelines during prosecution, which provides such a definition. (Pascal Decl., Exh. 1 ['612 Patent], at 8 (citing Bruce D. Cheson et al., *National Cancer Institute—Sponsored Working Group Guidelines for Chronic Lymphocytic Leukemia: Revised Guidelines for Diagnosis and Treatment*, 87 BLOOD 4990 (1996)).) The Guidelines explain that "[r]esponses that should be considered clinically beneficial include CR [complete remission], nPR [nodular partial remission] and PR [partial remission]; all others, e.g. stable disease, nonresponse, progressive disease, and death from any cause, should be rated as treatment failure." (Coutré Decl., Exh. C, at BID0001050, § 5.5.)

1. Specification

To construe "effective to treat the chronic lymphocytic leukemia," the Court will first look to the specification. The specification provides several examples which are "intended to provide clinical evidence in support of the efficacy of the invention." (Pascal Decl., Exh. 1 ['612 Patent], at 4:23–25.) In Example 1, four of the described patients experienced a reduction in circulating tumor cells. (*Id.* at 4:44–46.) The treatment of these four patients was ineffective, however, as they did not also experience a positive clinical benefit; they experienced severe toxic reactions to the anti-CD20 antibody, including fever, rigors, and bronchospasm with associated hypoxemia, and required hospitalization. (*Id.* at 4:40–55.) Although Defendants argue that the administration of anti-CD20 antibodies can cause infusion-related reactions in over 25% of cases in clinical trials, Example 1 describes the patients' reaction as a "unique syndrome of severe infusion-related reactions." (*Id.* at 4:41–42.) In addition, "[t]hrombocytopenia, a finding *not* commonly associated with RITUXAN® (rituximab) therapy, was noted in all four patients . . . , requiring transfusion in one case." (*Id.* at 4:48–53 (emphasis added).) These ineffective treatments are contrasted with "[t]wo subsequent

patients with CLL [who] have been treated with high blood tumor counts utilizing stepped-up dosing . . . with *demonstrated efficacy*, thrombocytopenia but minimal infusion-related toxicity." (*Id.* at 4:56–60 (emphasis added).)[5]

Example 3 provides an example of effective treatment of CLL. In this example, "[o]ne patient ha[d] progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes." (*Id.* at 6:24–27.) Although "[t]wo patients developed severe hypertension with the first dose," "[t]oxicity at subsequent escalated dosages has been mild." (*Id.* at 6:18–20.) In addition, one patient achieved full remission, a positive clinical benefit. (*Id.* at 6:24.) In addition, Example 5 describes a clinical study for CLL patients combining administration of the anti-CD20 antibody with chemotherapy. (*Id.* at 7:5–55.) The goals of this study were "complete response (CR)," "partial response (PR)," and achieving progression-free survival and overall survival—all positive clinical benefits. (*Id.* at 7:41–55.)

Defendants point to U.S. Patent No. 5,736,137, which is incorporated by reference into the specification of the '612 patent. (*See id.* at 3:23–24.) The '137 patent describes the effective treatment of B-cell disorders with anti-CD20 antibodies as including the depletion of peripheral blood B-cells and the depletion of B-cells from lymph nodes and other tissue sources. (Def. Op. Br., Exh. N ['137 Patent], at 8:49–56 ("[A] series of events take place, each event being viewed by us as important to effective treatment of the disease. The first 'event' then, can be viewed as principally directed to substantially depleting the patient's peripheral blood B cells; the subsequent 'events' can be viewed as either principally directed to simultaneously or serially clearing remaining B cells from the system.").) Defendants argue that this demonstrates that depletion of B-cells is a key event to treating B-cell cancers, including CLL. Defendants are correct that depletion of tumor cells is a key event in treating CLL. This does not mean, however, that effective treatment of CLL does not also require a positive clinical benefit.

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[5] Defendants point to the Applicants' statement to the PTO that "the specification provides at least two examples with report data from *in vivo* trials to illustrate the efficacy of the antibody treatment for patients suffering from hematological malignancies," citing to Examples 1 and 3. (Def. Op. Br., Exh. A-13, at BID0005177–78.) This Amendment and Reply, however, is dated August 29, 2000. This was before the claims were amended in August 2006 by replacing "effective to achieve a reduction in circulating tumor cells" with "effective to treat the chronic lymphocytic leukemia." The Amendment and Reply is therefore not relevant to this analysis.

Defendants also point to various sections of the specification that describe the invention as treating malignancies associated with circulating blood tumor cells, through administration of a therapeutically effective amount of rituximab. (Pascal Decl., Exh. 1 ['612 Patent], at cover, 1:1–5, 15–20, 58–61; 2:16–20, 35–38; 3:48–54.) It is true that the '612 patent treats malignancies associated with circulating blood tumor cells, through administration of a therapeutically effective amount of rituximab. Specifying that the invention calls for the administration of a "therapeutically effective" amount of rituximab, however, does not imply that effective treatment of CLL includes *only* the reduction of circulating tumor cells, and not a positive clinical benefit. In addition, many of the portions of the specification to which Defendants cite refer to the originally filed, but later cancelled, claims. Statements in the specification relating to limitations in originally-filed claims are not relevant when the claims as issued recite no such limitation. *Spine Solutions, Inc. v. Medtronic Sofamor Danek USA, Inc.*, 620 F.3d 1305, 1315 (Fed. Cir. 2010).

2. Prosecution History

Second, the Court will look to the prosecution history. As originally filed in 1999, claim 1 read: "A method of treating a *hematologic malignancy* associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of an anti-CD20 antibody or fragment thereof." (Pascal Decl., Exh. 5, at BID0004763.) On August 29, 2000, claim 1 was amended in response to a rejection. As amended, claim 1 read: "A method of treating *hematologic malignancy* associated with high numbers of circulating tumor cells by administering a therapeutically effective amount of an anti-CD20 antibody or antigen binding fragment thereof, said amount being *effective to achieve a reduction in circulating tumor cells*." (*Id.*, Exh. 13, at BID0005168 (emphasis added).) The goal of the claims early in the prosecution history, therefore, was to (1) treat a broad range of blood cancers, and (2) achieve a reduction in circulating tumor cells.

On August 7, 2006, in response to the Examiner's rejection of the claims as filed, the Applicants cancelled the claims for treating hematologic malignancies and replaced them with a new set of claims directed toward the treatment of CLL. The new claims required treatment to be "effective to treat the chronic lymphocytic leukemia," rather than "effective to achieve a reduction in circulating tumor cells." For instance, new application claim 29, which was issued as claim 1, read: "A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an unlabeled

anti-CD20 antibody to the patient in an amount *effective to treat the chronic lymphocytic leukemia.*" (*Id.*, Exh. 5, at BID0004751 (emphasis added).) In this response, the Applicants explained to the Examiner the difference between the original claims and amended claims: "The new claims also differ from the claims they replace in that the amount of anti-CD20 antibody administered to the patient is required to be 'effective to treat the chronic lymphocytic leukemia,' instead of 'effective to achieve a reduction in circulating tumor cells.'" (*Id.* at BID0004763.)[6]

In a May 29, 2009 Reply to the PTO, the Applicants further explained that "effective treatment of CLL must result in a *positive clinical benefit* to the CLL patient. . . . [T]he claims do require a specific, positive therapeutic outcome, and not simply induction of any type of response in the patient." (*Id.*, Exh. 3, at BID0000278 (emphasis added) (internal quotation marks omitted).) The Applicants went on to distinguish this limitation from an ineffective treatment described by Jensen in a 1998 scientific article[7] on treating CLL. (*Id.*) In *Jensen*, a CLL patient showed signs of progression of the disease, exhibited a severe adverse reaction, and had to be treated by a different therapy. (*Id.*, Exh. 6, at BID0000319–21.) The Applicants explained that "the requirements of the claims are not met by *Jensen*, as by no measure can an undesirable and life-threatening condition in the CLL patient, coupled with a continued progression of the CLL disease be considered an effective treatment of CLL." (*Id.*, Exh. 3, at BID0000278 (internal quotation marks omitted).)[8]

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[6] Defendants cite this August 2006 response as well, pointing out that the Applicants stated that their proposed claims are "directed specifically to the treatment of CLL" and that one skilled in the art "would understand that effective treatments of CLL include, but are *not necessarily limited to*, those assessed with respect to a reduction in circulating tumor cells." (Def. Op. Br., Exh. E, at BID0004763 (emphasis added).) This statement does not contradict Plaintiffs' construction; Plaintiffs do not argue that "effective to treat the chronic lymphocytic leukemia" does *not* include a reduction in tumor cells, but rather that it *also* includes a positive clinical benefit. In addition, as explained above, this same response makes clear that the new claims were directed to a new goal, different from "a reduction in circulating tumor cells." (*Id.*)

[7] M. Jensen et al., *Rapid Tumor Lysis in a Patient with B-Cell Chronic Lymphocytic Leukemia and Lymphocytosis Treated with an Anti-CD20 Monoclonal Antibody (IDEC-C2B8, Rituximab)*, 77 ANN HEMATOL 89 (1998).

[8] Defendants argue that each of the patients discussed in *Jensen* received rituximab in dosages claimed in the '612 patent. The patent, however, does not contemplate the same dosages being effective for every patient. The specification explains, "[e]ffective dosages will depend on the specific antibody, condition of the patient, age, weight, or any other treatments, among other factors. Typically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight." (Pascal Decl., Exh. 1 ['612 Patent], at 3:48–54.)

Attached to this May 2009 Reply to the PTO, the Applicants included a declaration from Dr. David Schenkein, a practicing hematologist/oncologist at the time of the invention. Dr. Schenkein explained that "in an amount effective to treat the CLL" means that "the treatment must result in a positive clinical benefit to the CLL patient," and "refers to treatment methods that result in, for example, demonstrated efficacy with minimal infusion-related toxity . . . , overall response rate (ORR), complete responses (CR), partial responses (PR), improved median time to progression or improved duration of response . . . , or remission upon treatment." (*Id.*, Exh. 7, at BID0000293–94, ¶¶ 33–34.) Each of these examples cites to relevant descriptions in the specification. (*Id.*)

The PTO eventually issued the '612 patent, which contained claims directed toward methods of "administering an anti-CD20 antibody to the patient in an *amount effective to treat the chronic lymphocytic leukemia*." (*Id.*, Exh. 1 ['612 Patent], at 7:64–66 (emphasis added).) The prosecution history, therefore, supports construing the term "effective to treat the chronic lymphocytic leukemia" as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient." *See Festo Corp. v. Shoketsu Kinzoku Kogyo Kabushiki Co., Ltd.*, 535 U.S. 722, 733–34 (2002) ("[C]laims are interpreted by reference to those that have been cancelled or rejected. . . . [B]y the amendment the patentee recognized and emphasized the difference between the two phrases, and the difference which the patentee thus disclaimed must be regarded as material." (internal quotation marks omitted)).

Defendants point to various sources that they argue support their proposed construction. Many of the sources Defendants cite, however, should not be considered by the Court. For instance, Defendants cite the August 2000 Amendment and Reply. This Amendment and Reply relate to the cancelled claims, which contain the "effective to achieve a reduction in circulating tumor cells" language. (*See* Def. Op. Br., Exh. A-13, at BID0005168.) In addition, Defendants cite an email written by Dr. John Byrd (who is not an inventor of the '612 patent), a scientific meeting abstract written by Byrd and inventor Christine White (among others), and a scientific article written by Byrd and White (among others). (*Id.*, Exhs. G, H, I.) These sources, however, are extrinsic evidence that should not be considered if the ambiguity in the claim terms is resolved by the intrinsic evidence. *See Vitronics*, 90 F.3d at 1583 (explaining that if the intrinsic evidence resolves the ambiguity in the disputed claim terms, then "it is improper to rely on extrinsic evidence"); *N. Am. Vaccine, Inc. v. Am. Cyanamid Co.*, 7 F.3d 1571, 1578 (Fed. Cir. 1993) ("A patent is to be interpreted by what it states

rather than by what the inventor wrote in a scientific publication."); *Saso Golf, Inc. v. Nike, Inc.*, No. 08 C 1110, 2010 WL 4481772, at *3 (N.D. Ill. Nov. 1, 2010) (disregarding statements by third parties in its claim construction analysis).

Finally, Defendants argue that Plaintiffs' proposed construction is untenable. Defendants argue that other courts have rejected claim constructions that require a clinical response in a patient. None of the cases Defendants cite support this proposition, however. The courts in two of the cases Defendants cite chose constructions that were specific to the statements made in the specification and prosecution history for the patents at issue there, and so are not applicable to the present case. *See Amgen Inc. v. Hoechst Marion Roussel, Inc.*, 457 F.3d 1293, 1300–03 (Fed. Cir. 2006); *Wyeth v. Abbott Labs.*, No. 08-230 (JAP), 08-1021 (JAP), 2010 WL 3001913, at *6–7 (D. N.J. July 28, 2010). In addition, *Seroctin Research & Technologies v. Unigen Pharmaceuticals* supports Plaintiffs' proposed construction, as the court construed the term "therapeutically effective amount" as "a quantity that produces a *positive result* in the treatment of depression/mood disorders." *Seroctin Research & Techs. v. Unigen Pharm.*, No. 2:07-cv-00582-TC, 2008 WL 4866008, at *3 (D. Utah Nov. 10, 2008) (emphasis added).

In light of both the specification and the prosecution history,[9] the term "effective to treat the chronic lymphocytic leukemia" shall be construed as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient."

B. "Anti-CD20 Antibody" / "CD20-Binding Fragment"

The parties dispute the terms "anti-CD20 antibody" and "CD20-binding fragment." Plaintiffs propose that "anti-CD20 antibody" should be construed as "an antibody that binds to a cell surface CD20 antigen," and "CD20-binding fragment" should be construed as "a portion of an anti-CD20 antibody that binds to a cell surface CD20 antigen." Defendants propose that "anti-CD20 antibody" should be construed as "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," and "CD20-binding fragment" should be construed as "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with

[9] Both Plaintiffs and Defendants also point to extrinsic evidence in support of their proposed constructions. As the intrinsic evidence resolves the ambiguity in the claim terms, however, extrinsic evidence need not be considered.

similar affinity and specificity as rituximab."

The claims and the specification do not provide much guidance for whether the terms refer to an antibody or fragment thereof that binds to a particular epitope of the CD20 antigen with a particular affinity and specificity. The specification explains that the invention "provide[s] a novel treatment for . . . chronic lymphocytic leukemia (CLL) . . . comprising the administration of an anti-CD20 antibody." (Pascal Decl., Exh. 1 ['612 Patent], at 2:4–8.) The anti-CD20 antibody binds CD20, a protein found on the surface of the B lymphocytes. (*Id.* at 1:23–28.) The anti-CD20 antibody may be chimeric, primate, primatized, human, or humanized.[10] (*Id.* at 2:48–50.) "In the preferred embodiment, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from 10^{-5} to 10^{-9} M." (*Id.* at 2:45–47.) In addition, "a particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab)." (*Id.* at 3:18–19.) However, the Court may not "read[] limitations into a claim from the preferred embodiment described in the specification, even if it is the only embodiment described, absent clear disclaimer in the specification." *In re Am. Acad. of Sci. Tech Ctr.*, 367 F.3d 1359, 1369 (Fed. Cir. 2004).

The clearest evidence of the meaning of "anti-CD20 antibody" and "CD20-binding fragment" comes from the prosecution history. In a February 2000 Office Action, the PTO rejected claims 1 to 12 under 35 U.S.C. § 112 because "the specification, does not reasonably provide enablement commensurate with the scope of the claimed invention." (Pascal Decl., Exh. 12, at BID0005239.) Under Section 112,

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same, and shall set forth the best mode contemplated by the inventor of carrying out his invention.

35 U.S.C. § 112. In explanation, the Examiner pointed to the seemingly broad definition of "anti-CD20 antibody" and "CD20-binding fragment" in the specification. First, the Examiner explained that "Claims 1 and 12 are broadly drawn to '. . . an anti-CD20 antibody or fragment therefore'. This is broadly interpreted for examination purposes to be any and all anti-CD20 antibodies, no matter the

[10] A "humanized antibody" is a mostly human antibody with some non-human parts.

specificity or affinity for the specific epitope on the circulating tumor cells. While the specification is enabling for the application of RITUXAN®, RITUXIMAB® and 2B8-MX-DTPA in the treatment of hematologic malignancies, the specification is not enabling in the application of all other anti-CD20 antibodies, which may have different structural and functional properties." (Pascal Decl., Exh. 12, at BID0005239.) Second, the Examiner noted that "[t]he specification is silent concerning what sort of specificity and affinity would be necessary for the antibodies of the claimed passive immunotherapy so that one skilled in the art would not be able to practice the claimed invention without undue experimentation." (*Id.*)

In their August 29, 2000 Amendment and Reply, the Applicants traversed the rejection by arguing that they understood that the claim language did *not* encompass all anti-CD20 antibodies, but rather was limited to antibodies with a specificity and affinity similar to Rituxan. The Applicants argued that "even though antibodies directed to the same antigen might have different affinities and functional characteristics, one of skill in the art could readily identify an antibody that binds to CD20 with similar affinity and specificity as does RITUXAN® using techniques that are well known in the art." (*Id.*, Exh. 13, at BID0005174.) In addition, the Applicants pointed out that "the specification defines the preferred antibody . . . as one that binds CD20 with an affinity ranging from 10^{-5} to 10^{-9} M. Moreover, it is clear from the disclosure that the specificity must be such that antibody therapy results in a reduction of circulating tumor cells. Thus, the affinity and specificity of the antibodies to be used in the present invention are made clear in the disclosure." (*Id.* at BID0005175–76.)[11] The Examiner accepted these arguments, and in the next substantive Office Action withdrew the rejection. (*Id.*, Exh. 14, at BID0005125.) The prosecution history establishes that "anti-CD20 antibody" and "CD20-binding fragment" are defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab. *See Teleflex, Inc. v. Ficosa N. Am. Corp.*,

[11] Plaintiffs argue that in this same response, the Applicants explained that many types of anti-CD20 antibodies could be made for use with the invention, including chimeric, primate, primatized, humanized, and human antibodies. (Pascal Decl., Exh. 13, at BID0005176.) In addition, the Applicants stated that "the novelty of the presently claimed invention does not lie in a method of making therapeutic antibodies (although antibodies to be designed in the future for use in the claimed methods would certainly be encompassed)." (*Id.*) These statements, however, refer to the methods for producing chimeric, primate, primatized, humanized, and human antibodies. They do not establish that the claim language encompasses antibodies that bind with a different affinity and specificity than Rituximab, especially when considered in the context of the entire response.

299 F.3d 1313, 1326 (Fed. Cir. 2002) (holding that the prosecution history may "limit[] the interpretation of claims so as to exclude any interpretation that may have been disclaimed or disavowed during prosecution in order to obtain claim allowance" (internal quotation marks omitted)).

First, Plaintiffs argue that because claims 11, 12, and 14 are limited to chimeric antibodies, rituximab, and human antibodies, respectively, the independent claims—such as claim 1—are necessarily broader and not limited to these types of antibodies. (*See* Pascal Decl., Exh. 1 ['612 Patent], at 8:31–32, 33–34, 37–38.) It is true that "dependent claims are presumed to be of narrower scope than the independent claims from which they depend under the doctrine of claim differentiation." *Regents of Univ. of Cal. v. Dakocytomation Cal., Inc.*, 517 F.3d 1364, 1375 (Fed. Cir. 2008) (internal quotation marks omitted). On the other hand, "the presumption created by the doctrine of claim differentiation is not a hard and fast rule and will be overcome by a contrary construction dictated by the written description or prosecution history." *Id.* (internal quotation marks omitted). In this case, any presumption created by the doctrine of claim differentiation is overcome by the construction dictated by the prosecution history discussed above.

Second, Plaintiffs point to prior art in support of their construction. For one, Plaintiffs point to U.S. Patent No. 5,736,137, incorporated by reference into the '612 patent at 3:23–24. (Pascal Decl., Exh. 15.) Plaintiffs argue that the '137 patent did not limit the definition of anti-CD20 antibody to Rituxan and other antibodies that bind a particular epitope of the CD20 protein. During prosecution, however, the Applicants argued that using the invention described in the '137 patent, "the skilled artisan could readily produce anti-CD20 antibodies using similar techniques, and screen such antibodies for those having an *affinity and functional activity similar to RITUXAN®*." (*Id.*, Exh. 13, at BID0005174–75 (emphasis added).) In addition, Plaintiffs point to U.S. Patent No. 5,776,456 (*id.*, Exh. 16, at 6:60–64), U.S. Patent No. 5,843,439 (*id.*, Exh. 17, at 6:1–5), U.S. Patent No. 6,682,734 (*id.*, Exh. 18, at 5:66–6:3), and the Einfeld reference (*id.*, Exh. 19, at 711)—all considered by the PTO during prosecution— arguing that they provide definitions of "anti-CD20 antibody" that do not refer to a particular specificity, affinity, or epitope. These sources, however, do not exclude a particular specificity, affinity, or epitope from the definition of "anti-CD20 antibody."

Third, Plaintiffs argue that because claims may capture after-arising technology, if drafted broadly enough, the construction of "anti-CD20 antibody" and "CD20-binding fragment" is not limited

to anti-CD20 antibodies or fragments thereof that bind to the same epitope of the CD20 antigen as rituximab. In 1998, at the time of the invention, it was believed that CD20 had only one extracellular region, or epitope, (i.e., the "large loop") to which CD20 antibodies could bind. Consequently, all antibodies that bound with a similar affinity and specificity as Rituxan at the time of the invention would have been understood to bind to this epitope. Not until 2006 was it discovered that Arzerra, a human antibody, could bind to a previously unknown epitope of the CD20 antigen, with a different affinity and specificity than rituximab.[12] Whether claim language may encompass after-arising technology, however, is irrelevant here. The prosecution history establishes that "anti-CD20 antibody" and "CD20-binding fragment" is defined as anti-CD20 antibodies or fragments thereof that bind to the CD20 antigen with similar affinity and specificity as rituximab. Antibodies that bind to the CD20 antigen with similar affinity and specificity as rituximab bind to the "large loop." Accordingly, the terms "anti-CD20 antibody" and "CD20-binding fragment" shall be construed as "rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab" and "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," respectively.

C. "Does Not Include Treatment with a Radiolabeled Anti-CD20 Antibody" / "Radiation Is Not Used"

The parties dispute whether the terms "does not include treatment with a radiolabeled[13] anti-CD20 antibody" and "radiation is not used" should be construed. Plaintiffs propose that no construction of these two terms is necessary, and their plain and ordinary meanings should be used. Defendants propose that "does not include treatment with a radiolabeled anti-CD20 antibody" should be construed as "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody," and "radiation is not used" should be construed as "no form of radiation (including radiolabeled antibodies) is used."

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[12] In addition to binding the previously unknown epitope of the CD20 antigen, Arzerra also binds a portion of the "large loop" that Rituxan does not bind.

[13] A "radiolabeled antibody" is an antibody with a radioisotope attached to it. The radioisotope emits radiation.

Before amendment, pending claims 29 and 55 (issued claims 1 and 23) provided for the administration of an "unlabeled anti-CD20 antibody." (Def. Op. Br., Exh. B, at BID0001256, BID0001259.) The Examiner explained that pending claims 29 and 55, therefore, "could be interpreted to cover the administration of an unlabeled antibody followed by a radiolabeled antibody." (*Id.* at BID0001265.) The Applicants "discussed possible ways to amend the claims to exclude such a possibility." (*Id.*) "The examiner indicated amending the claims to exclude a step of administering a radiolabeled antibody would address the Office's concerns." (*Id.*)

Pending claims 29 and 55 were amended to read: "A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient . . . , *wherein the method does not include treatment with a radiolabeled antibody.*" (*Id.* at BID0001256, BID0001259 (emphasis added).) The Applicants explained that "[pending] [c]laims 29 and 55 now require that the method does not include treatment with a radiolabeled antibody. This limitation expressly excludes the combination protocols described in the Kaminski patent, and it also precludes the use of a radiolabeled antibody as the anti-CD20 antibody of the recited administration step." (*Id.* at BID0001267.) The combination protocol described in the Kaminski patent includes the administration of an unlabeled antibody and the administration of a radiolabeled antibody. (*Id.* at BID0001269.) The claim language, therefore, excludes two separate treatments: (1) administration of an anti-CD20 antibody with a radiolabel attached to that antibody, and (2) administration of an anti-CD20 antibody that does not have a radiolabel along with the administration of a radiolabeled anti-CD20 antibody. Accordingly, the prosecution history supports Defendants' proposed constructions, "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody" and "no form of radiation (including radiolabeled antibodies) is used." *See Edwards Lifescis. LLC v. Cook Inc.*, 582 F.3d 1322, 1329 (Fed. Cir. 2009) (applicants' arguments made to examiner regarding claim scope in light of prior art are controlling).

Plaintiffs argue that construction of these claim terms is inappropriate because the claim terms are straightforward, Defendants' proposed constructions complicate the terms and add redundancies, and Defendants' proposed constructions improperly seek an advisory opinion as to whether use of Arzerra with Bexxar or Zevalin would infringe the '612 patent. On the contrary, if the claims are not

construed, it would be unclear whether it would be within the scope of the claims to administer an unlabeled antibody followed by a radiolabeled antibody. A construction reflecting the understanding of the Applicants and the Examiner that the claims do not cover the administration of an unlabeled anti-CD20 antibody along with the administration of a radiolabeled anti-CD20 antibody, is neither unnecessary or improper.

In addition, Plaintiffs argue that Defendants' construction improperly seeks to exclude the use of a radiolabeled anti-CD20 antibody at any time in the patient's history or future care. Plaintiffs explain that "'[e]xcludes' implies that the claimed method would *actively* exclude treatment with a radiolabeled anti-CD20 antibody, *i.e.*, a method that specifically instructs a user not to use a radiolabeled anti-CD20 antibody." (Pl. Op. Br. at 24.) On the contrary, the Applicants used the term "excludes" when discussing the amendment of pending claims 29 and 55 with the PTO. (Def. Op. Br., Exh. B, at BID0001267 ("[Pending] [c]laims 29 and 55 now require that the method does not include treatment with a radiolabeled antibody. This limitation expressly *excludes* the combination protocols described in the Kaminski patent, and it also precludes the use of a radiolabeled antibody as the anti-CD20 antibody of the recited administration step." (emphasis added)).) In addition, this interpretation of Defendants' construction is divorced from the claim language. The claims are directed toward the treatment of a patient with an anti-CD20 antibody, not toward the treatments of the patient over his entire lifetime. (*See* Pascal Decl., Exh. 22, at BID0000164 ("[Pending] [c]laims 29 and 55 are amended to specify the *treatments* do not include the administration of a radiolabeled anti-CD20 antibody." (emphasis added)); *Id.*, Exh. 1 ['612 Patent], at 2:35–40.) Accordingly, the terms "does not include treatment with a radiolabeled anti-CD20 antibody" and "radiation is not used" shall be construed as "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody," and "no form of radiation (including radiolabeled antibodies) is used," respectively.

CONCLUSION

For the reasons stated above, the term "effective to treat the chronic lymphocytic leukemia" shall be construed as "providing a positive clinical benefit to the chronic lymphocytic leukemia patient." The terms "anti-CD20 antibody" and "CD20-binding fragment" shall be construed as

"rituximab and antibodies that bind to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab" and "the portion of the anti-CD20 antibody that binds to the same epitope of the CD20 antigen with similar affinity and specificity as rituximab," respectively. Lastly, the terms "does not include treatment with a radiolabeled anti-CD20 antibody" and "radiation is not used" shall be construed as "excludes the use of a radiolabeled anti-CD20 antibody or the administration of a separate radiolabeled anti-CD20 antibody," and "no form of radiation (including radiolabeled antibodies) is used," respectively.

IT IS SO ORDERED.

DATED: October 17, 2011

HON. ROGER T. BENITEZ
United States District Court Judge


US007682612B1

(12) **United States Patent**
White et al.

(10) **Patent No.: US 7,682,612 B1**
(45) **Date of Patent: Mar. 23, 2010**

(54) **TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED WITH CIRCULATING TUMOR CELLS USING CHIMERIC ANTI-CD20 ANTIBODY**

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(*) Notice: Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 0 days.

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See application file for complete search history.

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(57) **ABSTRACT**

Chronic Lymphocytic Leukemia (CLL) may be treated with antibodies directed against the CD20 antigen.

60 Claims, No Drawings

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TREATMENT OF HEMATOLOGIC MALIGNANCIES ASSOCIATED WITH CIRCULATING TUMOR CELLS USING CHIMERIC ANTI-CD20 ANTIBODY

RELATED APPLICATIONS

This application claims benefit under 35 U.S.C. §119(e) to provisional application Ser. No. 60/107,658, filed Nov. 9, 1998, which is incorporated by reference in its entirety herein.

FIELD OF THE INVENTION

The present invention is directed to the treatment of hematologic malignancies associated with high numbers of circulating tumor cells by the administration of a therapeutically effective amount of a chimeric or humanized antibody that binds to the B-cell surface antigen Bp35 (CD20).

BACKGROUND OF THE INVENTION

The use of antibodies to CD20 as diagnostic and/or therapeutic agents for B-cell lymphoma has previously been reported. CD20 is a useful marker or target for B-cell lymphomas as this antigen is expressed at very high densities on the surface of malignant B-cells, i.e., those B-cells wherein unabated proliferation can lead to B-cell lymphomas.

CD20 or Bp35 is a B-lymphocyte-restricted differentiation antigen that is expressed during early pre-B-cell development and remains until plasma cell differentiation. It is believed that the CD20 molecule may regulate a step in the B-cell activation process which is required for cell cycle initiation and differentiation. Moreover, as noted, CD20 is expressed at very high levels on neoplastic ("tumor") B-cells.

Previous reported therapies involving anti-CD20 antibodies have involved the administration of a therapeutic anti-CD20 antibody either alone or in conjunction with a second radiolabeled anti-CD20 antibody, or a chemotherapeutic agent.

In fact, the Food and Drug Administration has approved the therapeutic use of one such therapeutic anti-CD20 antibody, RITUXAN® (rituximab), for use in treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma (NHL). Also, the use of RITUXAN® (rituximab) in combination with a radiolabeled murine anti-CD20 antibody has been suggested for the treatment of B-cell lymphoma.

However, while anti-CD20 antibodies and, in particular, RITUXAN® (rituximab) have been reported to be effective for treatment of B-cell lymphomas, such as non-Hodgkin's lymphoma, it would be beneficial if effective antibody treatments for other malignancies could be developed. More specifically, it would be beneficial if anti-CD20 antibodies could be used for treating other types of malignancies.

BRIEF DESCRIPTION OF THE INVENTION

Toward that end, the present inventors have developed a novel treatment for hematologic malignancies characterized by a high number of tumor cells in the blood involving the administration of a therapeutically effective amount of an anti-CD20 antibody. In the preferred embodiments, such anti-CD20 antibody will comprise a chimeric, humanized, or human anti-human CD20 antibody. Examples of such hematologic malignancies include B-pro-lymphocytic leukemia (B-PLL), chronic lymphocyte leukemia (CLL), and transformed non-Hodgkin's lymphoma.

Thus, it is an object of the invention to provide a novel treatment for hematologic malignancies comprising the administration of an anti-CD20 antibody.

It is a more specific object of the invention to provide a novel treatment for B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL) or transformed non-Hodgkin's lymphoma comprising the administration of an anti-CD20 antibody.

It is an even more specific object of the invention to treat B-prolymphocytic leukemia (B-PLL) or chronic lymphocytic leukemia (CLL) comprising administration of a therapeutically effective amount of RITUXAN® (rituximab).

DETAILED DESCRIPTION OF THE INVENTION

The invention involves the discovery that hematologic malignancies and, in particular, those characterized by high numbers of tumor cells in the blood may be effectively treated by the administration of a therapeutic anti-CD20 antibody. These malignancies include, in particular, CLL, B-PLL and transformed non-Hodgkin's lymphoma.

This discovery is surprising notwithstanding the reported great success of RITUXAN® (rituximab) for the treatment of relapsed and previously treated low-grade non-Hodgkin's lymphoma. In particular, this discovery is surprising given the very high numbers of tumor cells observed in such patients and also given the fact that such malignant cells, e.g., CLL cells, typically do not express the CD20 antigen at the high densities which are characteristic of some B-cell lymphomas, such as relapsed and previously-treated low-grade non-Hodgkin's lymphomas. Consequently, it could not have been reasonably predicted that the CD20 antigen would constitute an appropriate target for therapeutic antibody therapy of such malignancies.

Treatment of hematologic malignancy, such as CLL, B-PLL and transformed non-Hodgkin's lymphoma, according to the invention will comprise the administration of a therapeutically effective amount of an anti-CD20 antibody, which administration may be effected alone or in conjunction with other treatment(s), e.g., chemotherapy, radiotherapy (e.g., whole body irradiation, or treatment with radiolabeled antibodies). In addition, combination therapy with cytokines may be useful to upregulate CD20 on the surface of the lymphoma cells.

In the preferred embodiment, the anti-CD20 antibody will bind CD20 with high affinity, i.e., ranging from 10^{-5} to 10^{-9} M. Preferably, the anti-CD20 antibody will comprise a chimeric, primate, PRIMATIZED®, human, or humanized antibody. Also, the invention embraces the use of antibody fragments, e.g., Fab's, Fv's, Fab's, $F(ab)_2$, and aggregates thereof.

A chimeric antibody is intended to refer to an antibody with non-human variable regions and human constant regions, most typically rodent variable regions and human constant regions.

A PRIMATIZED® antibody refers to an antibody with primate variable regions, e.g., complementarity-determining regions (CDRs), and human constant regions. Preferably, such primate variable regions are derived from an Old World monkey.

A humanized antibody refers to an antibody with substantially human framework and constant regions, and non-human CDRs. "Substantially" refers to the fact that humanized antibodies typically retain at least several donor framework residues (of non-human parent antibody from which CDRs are derived).

Methods for producing chimeric, primate, PRIMATIZED®, humanized, and human antibodies are well known in the art. See, e.g., U.S. Pat. No. 5,530,101, issued to Queen et al, U.S. Pat. No. 5,225,539, issued to Winter et al, U.S. Pat. Nos. 4,816,397 and 4,816,567, issued to Boss et al, and Cabilly et al, respectively, all of which are incorporated by reference in their entirety.

The selection of human constant regions may be significant to the therapeutic efficacy of the subject anti-CD20 antibody. In the preferred embodiment, the subject anti-CD20 antibody will comprise human, gamma 1, or gamma 3 constant regions and, more preferably, human gamma 1 constant regions. The use of gamma 1 anti-CD20 antibodies as therapeutics is disclosed in U.S. Pat. No. 5,500,362, issued to Robinson et al.

Methods for making human antibodies are also known and include, by way of example, production in SCID mice, and in vitro immunization.

As noted, a particularly preferred chimeric anti-CD20 antibody is RITUXAN® (rituximab), which is a chimeric gamma 1 anti-human CD20 antibody. The complete nucleic acid sequence encoding this antibody and the corresponding amino acid sequences of the heavy chain and light chain variable domains may be found in U.S. Pat. No. 5,736,137, which is incorporated by reference in its entirety. This antibody, which is produced in a proprietary CHO cell expression system commercialized by IDEC Pharmaceuticals Corporation, may be made by a CHO cell transfectoma comprising the vector DNA present in the *E. coli* host cell deposited on Nov. 4, 1992, under the provisions of the Budapest Treaty at the American Type Culture Collection (ATCC), 10801 University Boulevard, Manassas, Va. 20110-2209, under accession no. 69119. This deposit was determined to be viable and will be replaced should it become non-viable during the term of deposit. This deposit was made irrevocably available upon issuance of U.S. Pat. No. 5,736,137 and is available without restriction from the ATCC. This deposit will also be available without restriction during the lifetime of any patent that may issue based on this application.

The subject anti-CD20 antibody will be administered by various routes of administration, typically parenteral. This is intended to include intravenous, intramuscular, subcutaneous, rectal, and vaginal administration, with intravenous infusion being preferred.

The anti-CD20 antibody will be formulated for therapeutic usage by standard methods, e.g., by addition of pharmaceutically acceptable buffers, e.g., sterile saline, sterile buffered water, propylene glycol, and combinations thereof.

Effective dosages will depend on the specific antibody, condition of the patient, age, weight, or any other treatments, among other factors. Typically effective dosages will range from about 0.001 to about 30 mg/kg body weight, more preferably from about 0.01 to 25 mg/kg body weight, and most preferably from about 0.1 to about 20 mg/kg body weight.

Such administration may be effected by various protocols, e.g., weekly, bi-weekly, or monthly, dependent on the dosage administered and patient response. Also, it may be desirable to combine such administration with other treatments, e.g., radioactive therapy, both targeted and non-targeted, chemotherapies, and lymphokine or cytokine administration, e.g., interleukins, interferons, TNFs, colony stimulating factors, etc.

Typically, treatment will be effected weekly, for about 2 to 10 weeks, more typically about 4 weeks. A particularly preferred dosage regimen will comprise administration of about 375 mg/m^2 weekly for a total of four infusions. Also, stepped-up dosing schedules may be even more preferable.

If radiation is used in conjunction with the therapeutic anti-CD20 antibody, it is preferred that an yttrium-labeled anti-CD20 antibody be utilized, such as the one disclosed in U.S. Pat. No. 5,736,137, incorporated by reference in its entirety herein. This antibody, [^{90}Y]-2B8-MX-DTPA, has reported efficacy in the treatment of B-cell lymphoma. The hybridoma that produces the 2B8 antibody was deposited at the American Type Culture Collection under accession no. HB 11388 on Jun. 22, 1993, under the provisions of the Budapest Treaty, and was made irrevocably available upon issuance of U.S. Pat. No. 5,736,137, without any restrictions. This hybridoma was found to be viable and will be replaced during the lifetime of any patent that issues based on this application, should it become non-viable.

A particularly preferred chemotherapeutic regimen that may be used in conjunction with the subject antibody immunotherapy comprises CHOP chemotherapy, which comprises the administration of a combination of cyclophosphamide, doxorubicin, vincristine, and prednisone. Other known chemotherapeutics include methotrexate, cisplatin, toremifene, and tamoxifen.

The following examples are not intended, nor are they to be construed, as limiting the invention. The examples are intended to provide clinical evidence in support of the efficacy of the invention.

EXAMPLE 1

Two patients in whom we noted rapid reduction of blood tumor cells, which was associated with severe pulmonary infusion-related toxicity and thrombocytopenia, were studied. Also, two additional patients were collected from physician-submitted reports of adverse events related to RITUXAN® (rituximab) treatment. Pretreatment characterization of these patients included a median age of 60 years (range 26-73) with the diagnosis of B-prolymphocytic leukemia (B-PLL), chronic lymphocytic leukemia (CLL), or transformed non-Hodgkin's lymphoma. All of these patients had elevated leukocyte counts as a consequence of blood tumor involvement, bulky adenopathy and organomegaly. All four patients developed a unique syndrome of severe infusion-related reactions characterized by fever, rigors, bronchospasm with associated hypoxemia, requiring temporary cessation of RITUXAN® (rituximab) therapy. Concurrent with these symptoms, a rapid decrement in circulating tumor cell load (mean pretreatment 98×10^3L; range 73-132 vs. mean post-treatment 11×10^3L; range 37-24.6) with mild electrolyte evidence of rapid tumor lysis was observed. Thrombocytopenia, a finding not commonly associated with RITUXAN® (rituximab) therapy, was noted in all four patients (mean pretreatment 145×10^3L; range 57-277 vs. mean post-treatment $Sn\times10^9$/L; range 2-120), requiring transfusion in one case. Symptoms of this syndrome required hospitalization but resolved with supportive care. Subsequent RITUXAN® (rituximab) treatment were well tolerated in all patients.

Two subsequent patients with CLL have been treated with high blood tumor counts utilizing stepped-up dosing (100 mg day 1 followed by the rest of therapy on day 1) with demonstrated efficacy, thrombocytopenia but minimal infusion-related toxicity. RITUXAN® (rituximab) administration in patients with hematologic malignancies who have blood tumor cell involvement may be associated with a higher frequency of severe initial infusion-related reactions and thrombocytopenia mandating careful clinical monitoring. Given the preliminary activity of RITUXAN® (rituximab) in these patients, future studies in CLL and PLL, utilizing a stepped-up dosing schedule, are to be conducted.

EXAMPLE 2

Unlabeled immunoglobulins (monoclonal antibodies, Mabs) are attractive for the treatment of NHL as they may: mediate cytotoxicity with complement (CDC) or effector cells (ADCC); effect apoptosis; be less toxic, less immunogenic and possibly more effective than toxin- or drug-conjugated Mabs; not require the complex procedures needed for radiolabeled Mab therapy (radioimmunotherapy, RIT), and not produce the myelosuppression typical of high-dose RIT.

Until recently, use of Mabs in the treatment of hematologic malignancies has been limited. However, the chimeric anti-CD20 Mab, RITUXAN® (rituximab), has a low toxicity profile and significant clinical efficacy and is now approved by the U.S. Food and Drug Administration (November 1997) and in the E.U. (June 1998) for the treatment of relapsed or refractory, low-grade or follicular (R-LG/F) NHL. In a single-agent phase III clinical trial, of 166 patients with R-LG/F NHL treated with RITUXAN® (rituximab) at 375 mg/m^2 weekly for four infusions (study 102-05), the overall response rate (ORR) was 48% (6% complete response (CR) and 42% partial response (PR)). Median time to progression for responders was 13.1 months and duration of response was 11.2 months. Median circulating B-lymphocyte counts dropped to zero following the first dose. CD3, CD4, CD8 and NK cell counts remained unchanged. B-cell recovery in peripheral blood began at 6-9 months and was complete by 9-12 months. No significant changes in serum complement levels were noted. The mechanism for action remains unresolved with CDC, ADCC, apoptosis and/or others being considered. In spite of the absence of a clinical/laboratory correlation, the contribution of CDC cannot be discounted. We have seen a correlation between higher absolute NK cell count at baseline and response to the Mab.

Cell Type	# Patients CR + PR	Abs. Count	# Patients NR	Abs. Count	P-value
NK	98	180	15	98	0.02
MK + ANC	98	185	15	102	0.02
ANC	101	3.7	15	3.4	0.40
CD3+	98	761	15	576	0.37
Platelets	101	187	15	206	0.32

Note: N = 166 patients from study 102-05, and 37 from 102-06. Abs. Count: NK, CD3 = cells/mm^3; ANC, Pts. = cells × 10^3/mm^3. P value for the difference between Abs. Counts.

ADCC may be an important mechanism for the clinical activity seen in patients treated with RITUXAN® (rituximab). Agents which enhance effector cell number and activity may synergize with the Mab. Studies of RITUXAN® (rituximab) in combination with cytokines, e.g., Il-2, G-CSF, GM-CSF, INF, are also ongoing.

EXAMPLE 3

Phase I/II Study of RITUXAN® (rituximab) in CLL

RITUXAN® (rituximab) is a monoclonal antibody targeting CD20 that has significant activity in the treatment of low-grade lymphoma (LGL). When given at a dosage of 375 mg/m^2 weekly for four weeks the response rate in relapsed patients was 43% (McClaughlin et al., KOO, Vol. 14, 1998). Patients with small lymphocytic lymphoma (SLL) had lower response rates (13%) than patients with other subtypes of LGL and lower serum levels of RITUXAN® (rituximab). Reduced response seen in SLL could be related to lower density of CD20 antigen and/or higher circulating B-cell counts. Both factors would be expected to impact (negatively) on response seen in CLL.

In an attempt to maximize activities in CLL we are conducting a Phase I/II study. All patients receive a first dose of 375 mg/m^2 to minimize infusion related side effects. Subsequent weekly dosages (3) remain the same but are given at an increased dose level. Sixteen patients have been treated at dosages of 500-1500 mg/m^2. Median age was 66 years (range, 25-78). Eighty-one percent had end-stage III-IV disease. Median white blood cell count was 40×10^9/L (range, 4-200), Hgb 11.6 g/dl (range, 7.7-14.7), platelets 75×10^9/L (range, 16-160), median β_2 microglobulin was 4.5 mg/L (range, 3.1-9.2). Median numbers of prior therapies was 2.5 (range 1-9). Sixty percent of patients were refractory to treatment. Two patients developed severe hypertension with the first dose (375 mg/m^2); another one received further therapy. Toxicity at subsequent escalated dosages has been mild although no patient at the 1500 mg/m^2 dose level has been fully evaluated. Eight patients have completed therapy (4 at 500 mg/m^2, 3 at 650 mg/m^2, 1 at 825 mg/m^2). One patient treated at 560 mg/m^2 achieved full remission. One patient has progressive lymphocytosis on treatment and all other patients had reduction in peripheral blood lymphocytosis but less effect on lymph nodes. Dose escalation studies are ongoing.

EXAMPLE 4

Use of Cytokines to Upregulate the Expression of CD20

Another approach to improving response in CLL patients is to upregulate the CD20 antigen using cytokines. In an in vitro study, mononuclear cells from CLL patients were incubated for 24 hours with various cytokines. Flow cytometry results showed significant up-regulation by IL-4, GM-CSF, and TNF-alpha. (Venugopal P, Sivaraman S, Huang X, Chopra H, O'Brein T, Jajeh A, Preisler H. Upregulation of CD20 expression in chronic lymphocytic leukemia (CLL) cells by in vitro exposure to cytokines. *Blood* 1998; 10:247a.) In fact, recent data suggest that the upregulation of CD20 observed on CLL cells may be limited to tumor cells (Venogopal et al. Poster—PanPacific Lymphoma meeting, June 1999. Cytokine-induced upregulation of CD20 antigen expression in chronic lymphocytic leukemia (CLL) cells may be limited to tumor cells). Preliminary data also suggest that interferon alpha also upregulates CD20 on CLL cells after only 24 hours when applied at a concentration of 500 to 1000 U/ml.

Thus, by administering certain cytokines to CLL patients prior to or concurrently with administration of RITUXAN® (rituximab), the expression of CD20 on the surface of malignant B-cells may be upregulated, thereby rendering CD20, as well as other cell surface markers such as CD19, a more attractive target for immunotherapy.

A collaborative study has been initiated to test for optimal cytokine doses for CD20 upregulation in vivo. The study protocol involves treating ten patients initially with GM-CSF at 250 mcg/m^2 SQ QD X 3, ten patients with IL-4 mcg/kg SQ QD X 3, and ten patients with G-CSF at 5 mcg/kg SQ QD X 3. Mononuclear cells will be separated by FICOLL® (sucrose-epichlorohydrin copolymer) Hypaque centrifugation

for apoptotic studies to determine if upregulation of CD20 translates to enhanced killing of tumor cells by RITUXAN® (*rituximab*).

EXAMPLE 5

Combination Antibody and Chemotherapy Protocol

Antibody treatment of CLL can be combined with other conventional chemotherapeutic treatments known to be useful for the treatment of CLL. The most frequently used single agent for CLL is chlorambucil (LEUKERAN®), given either as 0.1 mg/kg daily or 0.4 to 1.0 mg/kg every 4 weeks. Chlorambucil is often combined with oral prednisone (30 to 100 mg/m^2/d), which is useful in the management of autoimmune cytopenias. Cyclophosphamide is an alternative to chlorambucil, the usual dose being 1-2 g/m^2 every 3-4 weeks together with vincristine and steroids (e.g., COP regimen).

Various drug combinations have been used for CLL, including COP (cyclophosphamide, Oncovin, and prednisone), and CHOP (these three drugs plus doxorubicin). Fludarabine has shown an effect in the treatment of CLL, and gave an ORR of 50% in a group of patients treated with 25-30 mg/m^2/d every 3-4 weeks. See www.cancernetwork.com. Some patients have been shown to be refractory for fludarabine. Such patients may also be resistant to 2-CdA because often, patients who are refractory to fludarabine are also refractory to 2-CDA (O'Brien et al. N. Engl. J. Med. 330: 319-322 (1994)).

Hence, anti-CD20 antibody therapy will be particularly useful for patients who are refractory or who have relapsed after treatment with chemotherapeutic drugs. RITUXAN® (rituximab) therapy may also be combined with radiotherapy in these patients. TBI with a low fraction size of 15 cGy to total doses of 75 to 150 cGy has been shown to be effective in about one-third of patients.

A Phase II trial is currently being conducted by CALGB in CLL patients. RITUXAN® (rituximab) and fludarabine are administered concurrently, followed by RITUXAN® (rituximab) consolidation versus fludarabine induction followed by RITUXAN® (rituximab). The goals of the study are (1) to determine in fludarabine treated CLL patients the complete response (CR) rate and toxicity profile of concurrent and consolidative RITUXAN® (rituximab) therapy (Arm I) and of consolidative RITUXAN® (rituximab) therapy (Arm II); (2) to assess the CR rate in patients receiving concurrent therapy with RITUXAN® (rituximab) and fludarabine (the inductive phase of Arm I); (3) to assess the frequency of conversion of a partial response (PR) to a CR or stable disease to either PR or CR in CLL patients receiving consolidative therapy with RITUXAN® (rituximab); (4) to follow the effects of therapy with RITUXAN® (rituximab) and fludarabine on the immunologic markers CD4, CD8, IgG, IgA and IgM; and (5) to examine progression-free survival and overall survival in Arms I and II.

Although the present invention has been described in some detail by way of illustration and example, for purposes of clarity and understanding it will be apparent that certain changes and modifications may be practical within the scope of the appended claims.

What is claimed is:

1. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

2. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.

3. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.

4. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.

5. A method according to claim 1, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m^2.

6. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

7. A method according to claim 6, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2.

8. A method according to claim 1 or 6, wherein the patient has relapsed following previous treatment for the chronic lymphocytic leukemia.

9. A method according to claim 1 or 6, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

10. A method according to claim 9, wherein the patient is refractory to fludarabine.

11. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a chimeric antibody.

12. A method according to claim 11, wherein the anti-CD20 antibody is rituximab.

13. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a humanized antibody.

14. A method according to claim 1 or 6, wherein the anti-CD20 antibody is a human antibody.

15. A method according to claim 1 or 6, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.

16. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient repeatedly.

17. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly.

18. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.

19. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient biweekly.

20. A method according to claim 16, wherein the anti-CD20 antibody is administered to the patient monthly.

21. A method according to claim 1 or 6, wherein the anti-CD20 antibody is administered to the patient parenterally.

22. A method according to claim 21, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.

23. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody therapy is combined with chemotherapy, wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

24. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.001 to about 30 mg/kg.

25. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.01 to about 25 mg/kg.

26. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 0.1 to about 20 mg/kg.

27. A method according to claim 23, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 375 mg/m^2.

28. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 to about 1500 mg/m^2, wherein the anti-CD20 antibody therapy is combined with chemotherapy, and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

29. A method according to claim 28, wherein the anti-CD20 antibody is administered to the patient at a dosage of about 500 mg/m^2.

30. A method according to claim 23 or 28, wherein the patient has relapsed following previous treatment for the chronic lymphocytic leukemia.

31. A method according to claim 23 or 28, wherein the patient is refractory to a treatment previously administered for the chronic lymphocytic leukemia.

32. A method according to claim 31, wherein the patient is refractory to fludarabine.

33. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a chimeric antibody.

34. A method according to claim 33, wherein the anti-CD20 antibody is rituximab.

35. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a humanized antibody.

36. A method according to claim 23 or 28, wherein the anti-CD20 antibody is a human antibody.

37. A method according to claim 23 or 28, wherein the anti-CD20 antibody comprises a CD20-binding fragment of a chimeric, humanized, or human antibody.

38. A method according to claim 23 or 28, wherein the anti-CD20 antibody is administered to the patient repeatedly.

39. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient weekly.

40. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient weekly for about 2 to 10 weeks.

41. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient biweekly.

42. A method according to claim 38, wherein the anti-CD20 antibody is administered to the patient monthly.

43. A method according to claim 23 or 28, wherein the anti-CD20 antibody is administered to the patient parenterally.

44. A method according to claim 43, wherein the anti-CD20 antibody is administered to the patient by intravenous infusion.

45. A method according to claim 23 or 28, wherein the anti-CD20 antibody therapy and the chemotherapy are administered to the patient concurrently.

46. A method according to claim 23 or 28, wherein the chemotherapy comprises chlorambucil.

47. A method according to claim 23 or 28, wherein the chemotherapy comprises cyclophosphamide.

48. A method according to claim 47, wherein the chemotherapy comprises cyclophosphamide, vincristine, and prednisone (COP).

49. A method according to claim 47, wherein the chemotherapy comprises cyclophosphamide, vincristine, prednisone, and doxorubicin (CHOP).

50. A method according to claim 23 or 28, wherein the chemotherapy comprises vincristine.

51. A method according to claim 23 or 28, wherein the chemotherapy comprises prednisone.

52. A method according to claim 23 or 28, wherein the chemotherapy comprises doxorubicin.

53. A method according to claim 23 or 28, wherein the chemotherapy comprises fludarabine.

54. A method according to claim 23 or 28, wherein the chemotherapy comprises methotrexate.

55. A method according to claim 23 or 28, wherein the chemotherapy comprises cisplatin.

56. A method according to claim 23 or 28, wherein the chemotherapy comprises toremifene.

57. A method according to claim 23 or 28, wherein the chemotherapy comprises tamoxifen.

58. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering an anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein the patient is refractory to fludarabine previously administered for the chronic lymphocytic leukemia, and wherein the method does not include treatment with a radiolabeled anti-CD20 antibody.

59. A method according to claim 6, 28, or 58, wherein radiation is not used in conjunction with the anti-CD20 antibody.

60. A method of treating chronic lymphocytic leukemia in a human patient, comprising administering a therapeutic non-radiolabeled anti-CD20 antibody to the patient in an amount effective to treat the chronic lymphocytic leukemia, wherein radiation is not used in conjunction with said anti-CD20 antibody.

* * * * *

No. 2012-1120

In the United States Court of Appeals for the Federal Circuit

BIOGEN IDEC INC. and GENENTECH, INC.,

Plaintiffs-Appellants,

v.

GLAXOSMITHKLINE LLC and GLAXO GROUP LIMITED,

Defendants-Appellees.

Appeal From The United States District Court For The Southern District Of California In Case No. 10-CV-0608, The Honorable Roger T. Benitez.

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April 11, 2012

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OPENING BRIEF OF PLAINTIFFS-APPELLANTS BIOGEN IDEC INC. AND GENENTECH, INC.

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I declare that I caused to be filed via overnight courier the original and 13 copies of the above-listed document(s) in this matter with the Clerk of the United States Court of Appeals for the Federal Circuit this same day.

I declare that I am employed in the office of a member of the Bar of or permitted to practice before this Court at whose direction the service was made.

I declare under penalty of perjury under the laws of the United States of America that the above is true and correct. Executed on April 11, 2012, at San Diego, California.

Joyce Graham

CERTIFICATE OF COMPLIANCE
PURSUANT TO FED. R. APP. P. 32(a)(7)(C)

Pursuant to Federal Rule of Appellate Procedure 32(a)(7)(C), I certify that the attached Opening Brief of Plaintiffs-Appellants Biogen Idec Inc. and Genentech, Inc., is proportionally spaced, has a typeface of 14 points or more, and, as counted by the Microsoft Word program used to prepare the brief, contains 11,204 words.

Dated: April 11, 2012

Respectfully submitted,

Stanley J. Panikowski

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